# The American Journal of Medicine

April 1948

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# The American Journal of Medicine



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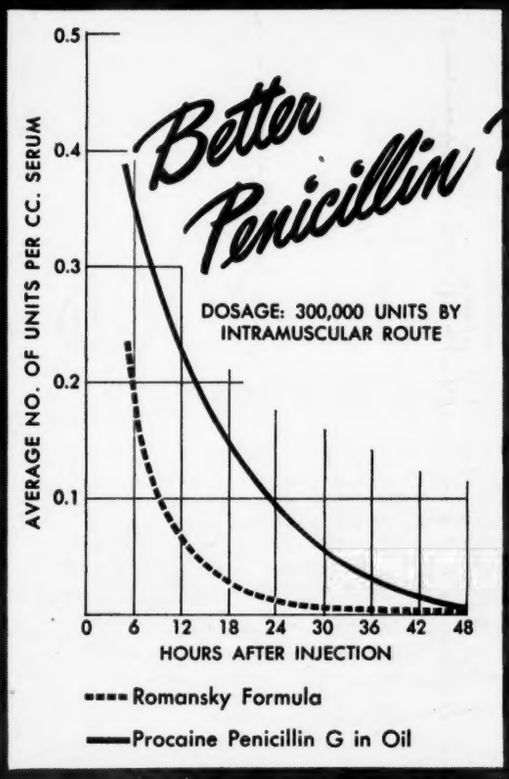


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fat infiltration
functional impairment
toxic hepatitis
infectious hepatitis

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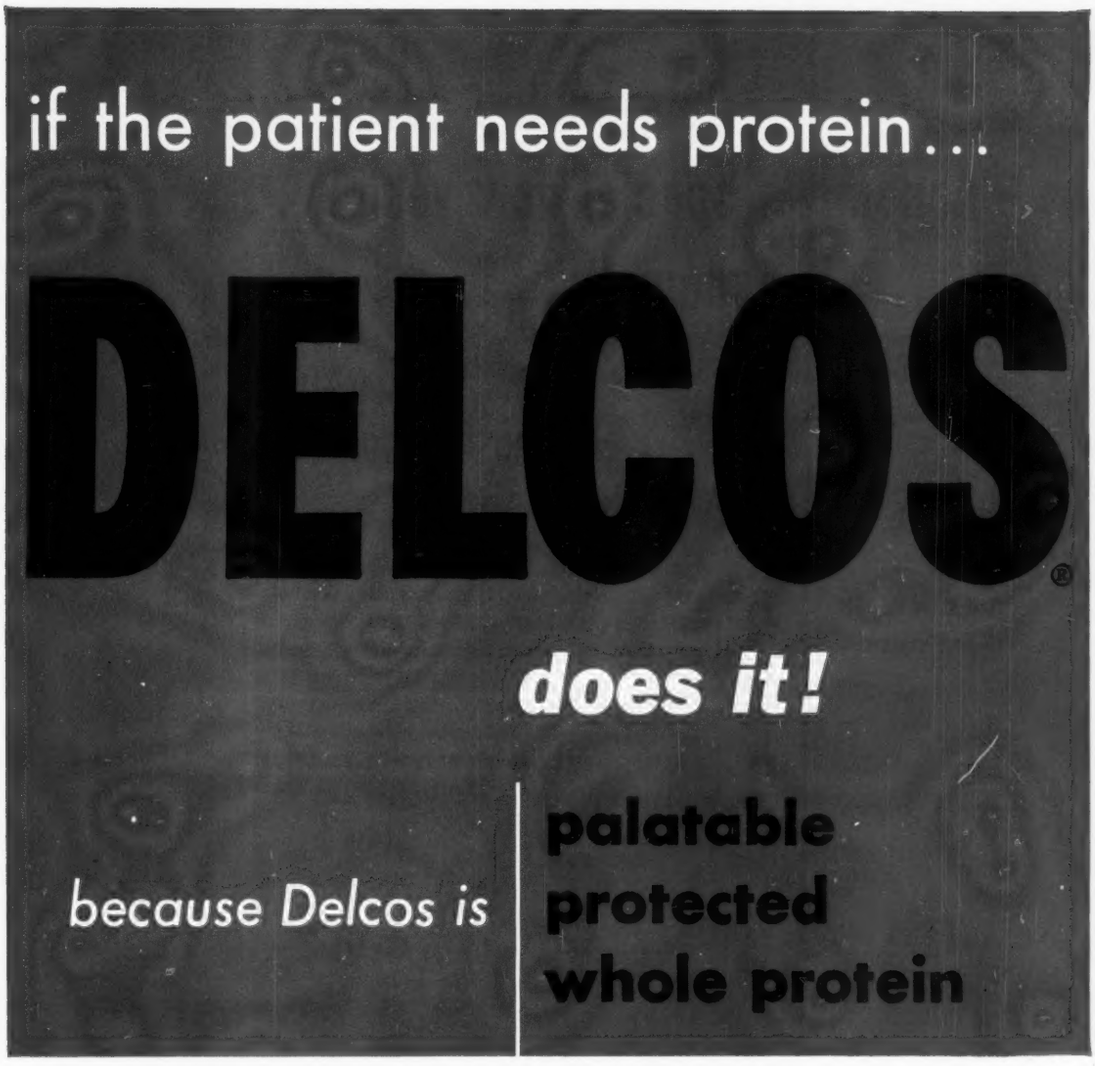


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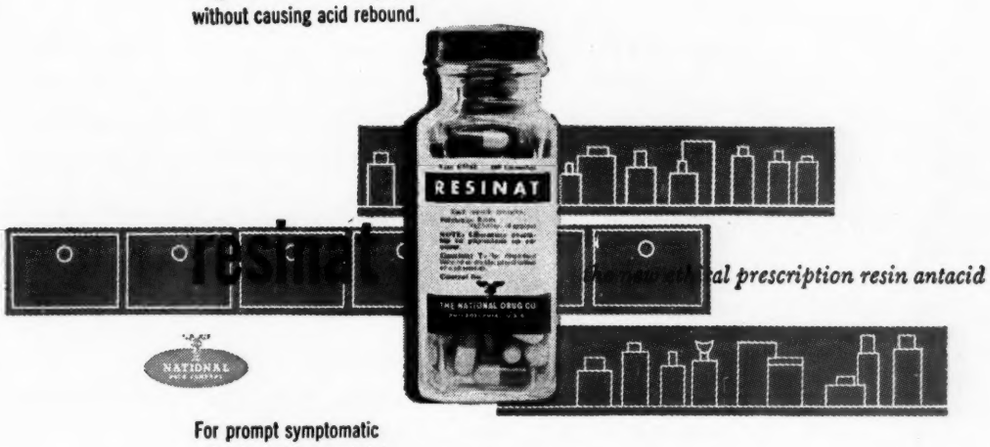


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Le Veen, H. W.: Gastroenterology, 8:648, 1947
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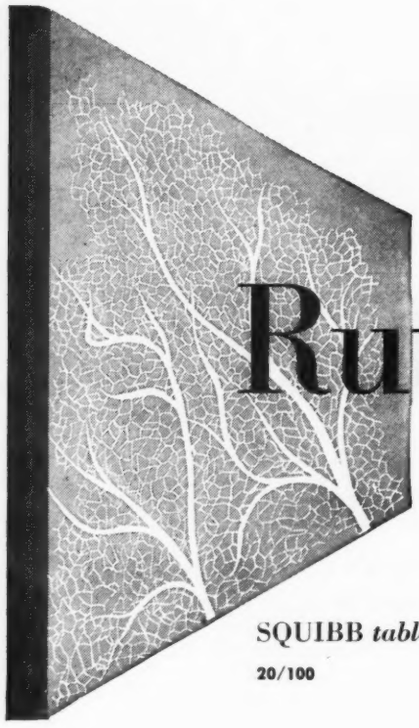
Spears, M. M. & Pfeiffer, M. C. J.: Gastroenterology, 8:191, 1947

*when vascular walls weaken*



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1. Couch, J. F., et al.: Bur. of Agric. & Indus. Chem., U. S. Dept. of Agriculture. AIC-115 (April) 1946. 2. Griffith, J. Q., Jr., and Lindauer, M.A.: Am. Heart J. **28**:758 (Dec.) 1944.

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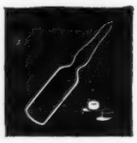

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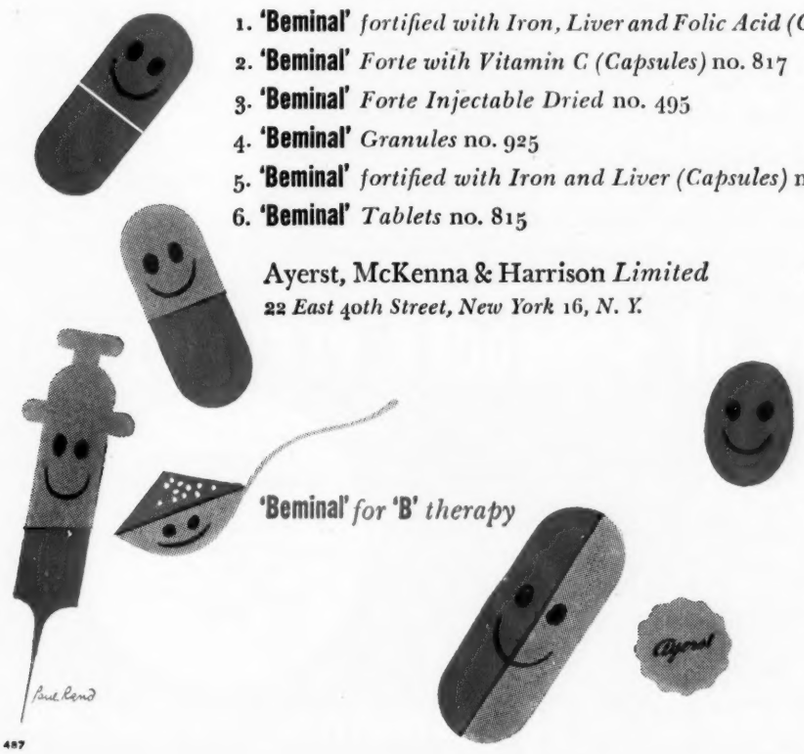


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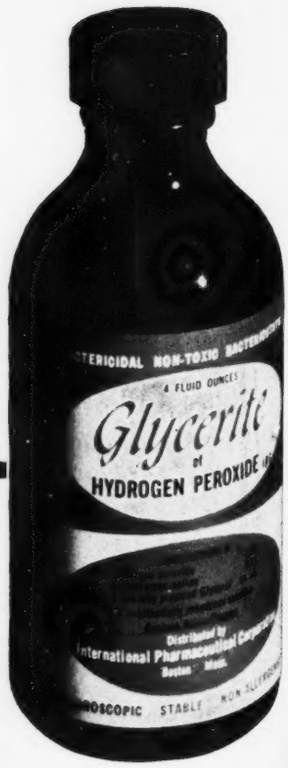


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New Eng. J. Med. 234:468, 1946.
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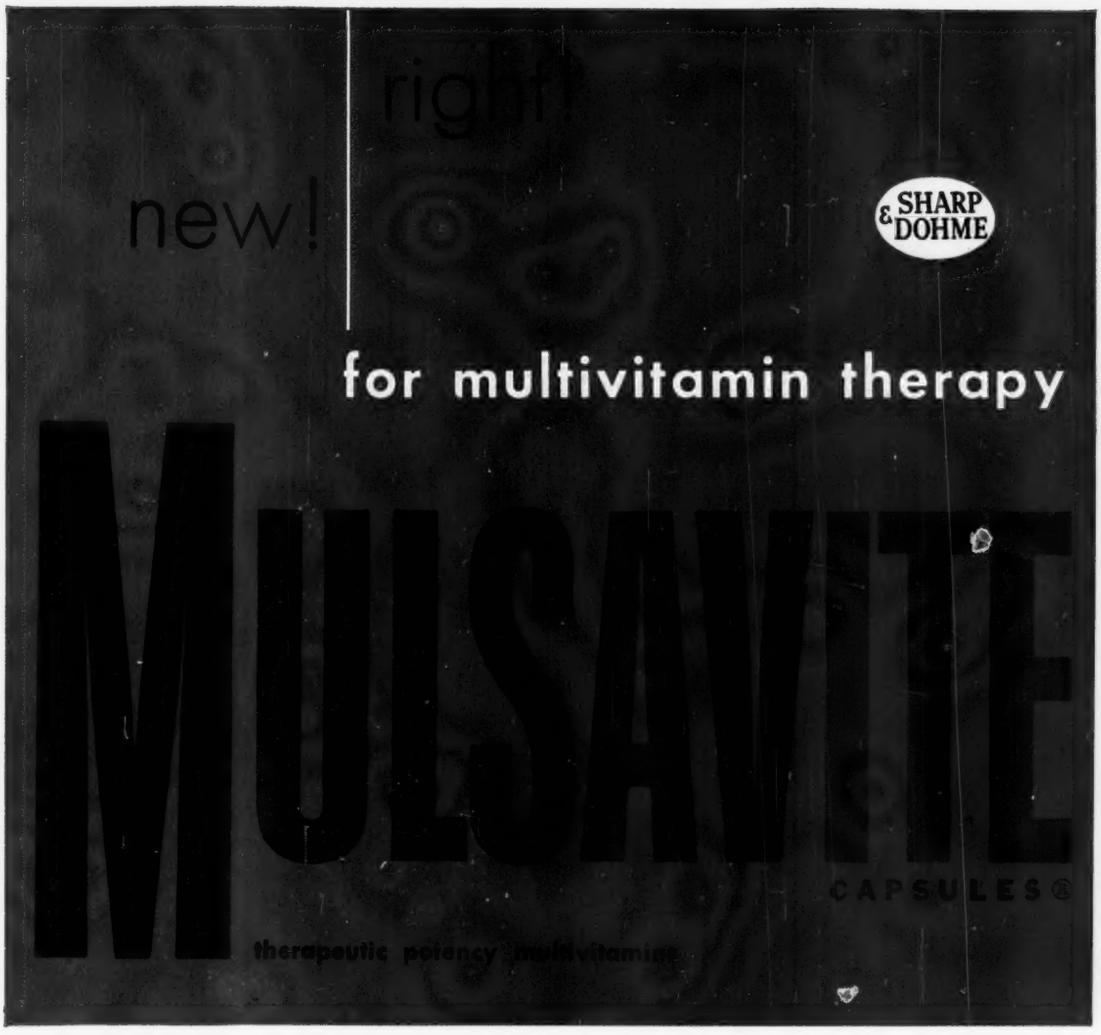


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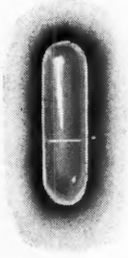

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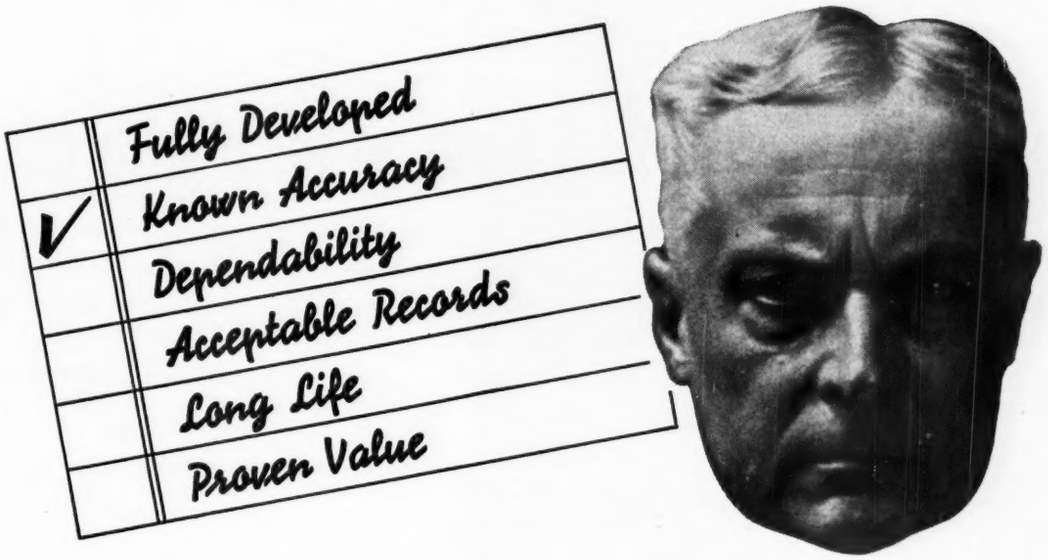


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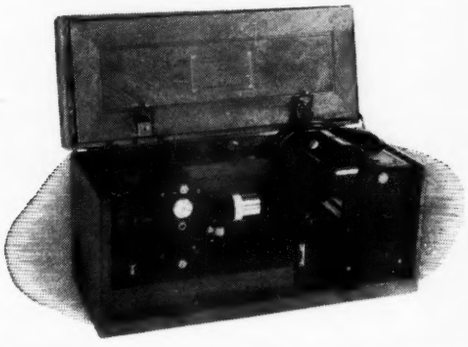

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# Editorial

## Cancer Research

CANCER is an inclusive expression which we use to cover many different diseases which have a common characteristic, namely, abnormal and invasive growth. Descriptive knowledge of cancer is elaborate, and we have practical means for alleviation and sometimes for cure in surgical extirpation and in radiation therapy. The pathologist, the surgeon and the radiologist are the clinical team which has been most concerned with diagnosis and treatment of the disease. More and more we can expect new developments, both in terms of diagnosis and treatment, to expand the groups having a very definite place in the total care of the cancer patient. All physicians, general practitioner and specialist alike, must concern themselves with this problem. The internist must become one of the key figures in interdisciplinary clinical and research efforts.

Research in experimental cancer is pointing to many complex host factors as a background in the development of tumors. Among these are endocrine dyscrasias and altered metabolism, which are linked to cancer in varying degrees and combinations. Present knowledge warrants the assumption that superimposed on local causative agents are complicated systemic alterations. We do not fully understand the significance of the mammary tumor agent, a probable virus, in breast cancer of certain strains of mice, nor of the implication of viruses in human breast or other cancers. There is thus a great need for participation in cancer control by more specialists than the three groups named. It is everyone's problem, not that of a few.

Early care of the patient by present means can save tens of thousands more lives each year than are now saved. But our final hope lies in research. Research in cancer has interested many workers in the fundamental sciences, and an ever widening search for basic information on cell growth and differentiation has been launched. Fundamental studies in the field of growth are worthy of extension on a much larger scale. More and more research directly on the problem of human cancer must be encouraged and increased. More studies should be made in man of enzyme systems, proteins, lipids and steroids, and of metabolism generally, including greater application of both stable and radioactive isotopes as tracers and as therapeutic agents alone and in combination with other materials. The search for cancer tests and cancer chemotherapeutic agents is so important that great expansion in scope is indicated.

The history of medicine points time and time again to the discovery of satisfactory methods of treatment or of cures in advance of the finding of answers to all fundamental and background aspects of various problems. It is foolhardy to predict that major answers in cancer research will come in such fashion, yet the possibility cannot be overlooked and we are warranted in pressing the more empirical research approach

to the problem as long as we do not let up on our fundamental studies.

What do we need in addition to that which we now have? We need the interest of more physician-investigators, and of other scientists skilled in all of the specialized fields of the medical and biologic sciences. We need more teachers of scientists and economic security for these teachers. We need to follow present leads and we need new research ideas. These will come as the scientist potential grows with the addition of "new blood." We need more teamwork and interdisciplinary effort. We need more laboratories and especially do we need more research beds with associated laboratories. We need more adequate, assured long range financing of men and of equipment, supplies and facilities (including research beds) by endowment and other philanthropy, by support by foundations and other voluntary agencies, and by government at all levels. Hektoen* once wrote "research in competent hands should not be restricted for want of anything which money can provide." The "competent hands" exist. The public, through the American Cancer Society and other voluntary agencies, and the Congress of the United States, have given liberal support to finance cancer research throughout the United States during the present year. Federal funds in the amount of $5,000,000 are available through the National Advisory Cancer Council of the National Cancer Institute, one-half to finance individual cancer research projects and one-half for laboratory and clinical research facility construction in non-Federal research centers. The Atomic Energy Commission has $5,000,000 earmarked by Congress for activities in the cancer field, part of which will be used for research grants. In addition there are extensive research fellowship programs in the National Cancer Institute and the Atomic Energy Commission. Large sums are available from the Committee on Growth of the National Research Council, acting for the American Cancer Society, and from other foundations and organizations to support research projects and research fellowships. In addition the American Cancer Society has embarked on a praiseworthy program of giving sizable "institutional" research grants. However, in spite of these programs there is not enough money available at the present time to support many worthy research projects. We are warranted in providing larger sums for cancer research than are now available, not only for the results which will come in solution of the cancer problem but also for the results which will be of value in better understanding of fundamental biology and of many diseases in addition to cancer.

The American public has indicated clearly its interest in greater research efforts in cancer. Physicians and other related professional groups must take up the challenge and drive intensively and relentlessly for greater and speedier progress in cancer research and control. Teamwork on the part of all professional and lay groups can go far to make the solution of the cancer problem a reality.

LEONARD A. SCHEELE, M.D.†
Surgeon General
United States Public Health Service

* HEKTOEN, LUDVIG. Progress Against Cancer. Pamphlet of American Medical Association, 1946.

† Formerly Director, National Cancer Institute.

# Clinical Studies

## Pneumonia and Erythema Multiforme Exudativum

### *Report of Four Cases and Three Autopsies*

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*and* FREDERIC PARKER, JR., M.D.

*Boston, Massachusetts*

THE vesicular or bullous type of erythema multiforme with severe systemic symptoms and involvement of the conjunctivae and the mucous membranes of the orificial surfaces has been considered to be rather rare.[1–4] Renewed interest in this condition, however, has recently brought forth a number of reports of such cases, occurring singly or in small groups, with lesions of varying extent and severity and considered under a variety of designations. In one hospital for contagious diseases thirty-three patients were seen over a period of thirteen years;[5,6] seventeen were encountered in Canadian military hospitals in a few months;[7] six cases which occurred over a period of three years were reported from Fort Bragg;[8] a series of twenty subjects with various combinations of lesions and observed over several years were reported from another military installation;[4] ten cases were studied in one large naval hospital[9] and two patients were admitted to a civilian general hospital only eighteen days apart.[10]

The milder forms of erythema multiforme exudativum and those with relatively few lesions are rather benign, but even with the more severe forms most of the patients recover with varying rapidity and without sequelae save for occasional instances of permanent and disabling damage to ocular structures.[3,4,6,11,12] Soll[4] stated that no deaths have been reported in English literature except for one questionable instance; Lever[3] collected only four fatal cases from the literature prior to 1944 but a larger number have since been reported. Thus there were five deaths among twenty-eight patients at the Willard Parker Hospital[5] and two deaths among the seventeen cases reported from the Canadian military hospitals.[7] Another fatal case in an American army hospital is mentioned in the report of the Commission on Acute Respiratory Diseases and at least two additional fatalities in patients with a similar syndrome following the use of sulfadiazine have also been recorded.[13,14]

The association of pulmonary lesions with erythema multiforme exudativum has recently been reviewed by the Commission on Acute Respiratory Diseases and lesions clinically resembling those of primary atypical pneumonia were reported in three of the six patients whom they observed at Fort Bragg.[8] Lesions of the respiratory tract including pneumonia were also frequent in the Canadian army cases and prompted the designation "mucosal respiratory syndrome."[7] Markham[15] described a fatal case of "atypical viral pneumonia" with super-

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imposed severe conjunctivitis, membranous stomatitis, bullous cutaneous eruption and balanitis and stated that four of five similar cases were fatal.

Cases presenting the characteristic picture of primary atypical pneumonia of unknown etiology,[16,17] particularly those of more than moderate severity, were recognized more frequently at the Boston City Hospital and in the surrounding communities during the fall and winter of 1942 to 1943 than at any other time before or since. The severity of these atypical pneumonias is attested by the occurrence of fifteen deaths in a group of 200 such cases that were studied between September 1942 and January 1944.[18] Early in the course of this outbreak a patient was admitted to the Boston City Hospital with the bullous type erythema multiforme with characteristic physical, x-ray and other findings of primary atypical pneumonia. The patient died and autopsy confirmed the findings in the lungs. Only three weeks later a second patient was admitted to the same medical service with very similar findings. This patient recovered but only after a very stormy course. Three months later a third patient with similar findings was admitted to another medical service; he also had a stormy course and, after a brief remission during which there was some improvement, a secondary bacterial infection of the cutaneous and pulmonary lesions set in and the patient died. Autopsy in this patient revealed evidence of both primary atypical pneumonia and of secondary necrotizing bacterial infection of the lungs.

Numerous other patients with primary atypical pneumonia of unknown etiology, of varying severity and associated with vesicular types of erythema multiforme were seen during this time and in the subsequent months through the courtesy of many physicians in civilian and military hospitals who were aware of our interest in such subjects. The patients that were seen, however, usually had very few lesions of the skin or mucous membranes and their illness was rather mild; none had the combination of a severe illness with widespread atypical pneumonia and extensive mucocutaneous lesions. Our attention was also called to a number of patients with erythema multiforme exudativum, many of them with ocular involvement, with lesions of the orificial surfaces and some of them acutely ill, but they did not have clinical or roentgenographic evidence of the characteristic and extensive pneumonitis and none of them were fatal.

The three cases cited appeared to be rather unique at the time and of considerable interest because of the association of extensive mucocutaneous and pulmonary manifestations. A fourth patient observed a few months later exhibited a fulminating course of the bullous type of erythema multiforme and autopsy revealed only minimal pulmonary lesions. In the latter case, and in the patient previously mentioned who recovered, there was a history of contact with dead birds. There was also serologic evidence suggestive of infection with a psittacosis-like virus in the patient who recovered and in the first fatal case. These unusual circumstances have prompted this report of the four cases, including the autopsies in the three fatal ones.

## CASE REPORTS

CASE I. A seventeen year old, white messenger boy was admitted to the Boston City Hospital, August 26, 1942, complaining of cough and sore throat. His illness began two weeks prior to entry with a cold, characterized by coryza and malaise, and a week later he developed a cough productive of gray sputum which persisted to entry. On the day before admission he first noted a severe sore throat with dysphagia and the sputum became stained with dark streaks of blood. That evening he had a shaking chill and began to experience some anterior chest pain with cough. He had received no sulfonamide drugs nor any other medication. Both family history and past history were non-contributory.

When first seen the patient was well developed and moderately well nourished, acutely ill and breathing rapidly. There was marked injection of the scleral and palpebral conjunctivae. The

lips were dry and cracked and covered with bloody crusts; on the buccal mucous membranes there were many vesicles from 2 to 8 mm. in diameter, some with clear fluid and others with hemorrhagic material and each surrounded with an area of intense erythema. The pharynx was diffusely red and covered with small patches of gray exudate. There were a number of scattered vesicles on the neck. Some of these had become pustular and others had a typical rosette appearance. There were a few small, firm, non-tender nodes felt in the submaxillary, anterior cervical and left axillary regions. In the lungs there were a few scattered crepitant râles and some inconstant, high-pitched, sibilant râles. There were also some areas of diminished breath sounds but no dullness. The heart sounds were rapid but otherwise normal. The rest of the examination was negative.

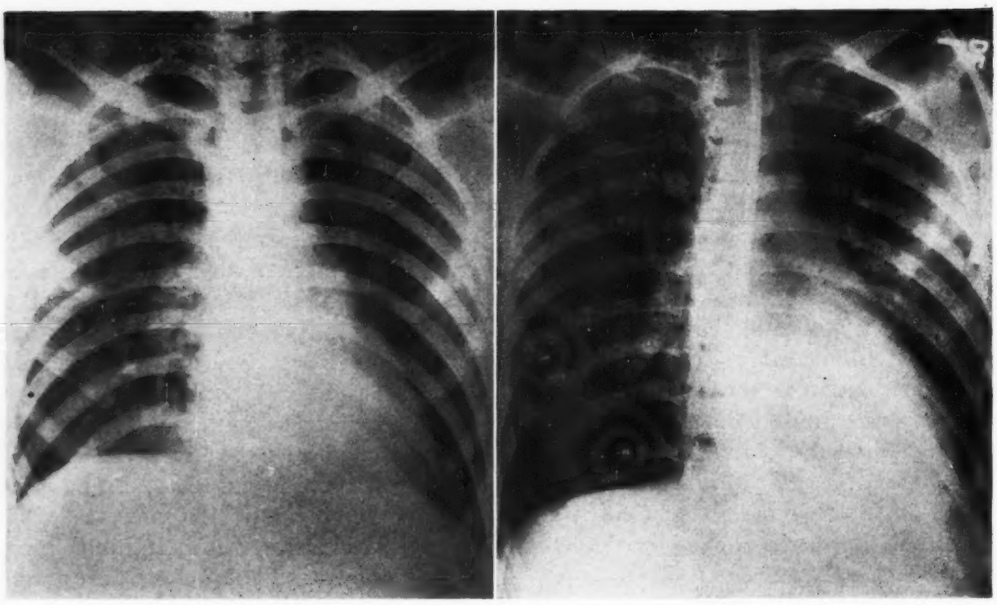
The hemoglobin was 86 per cent; red blood count 4,170,000 and white blood count 12,200 with 40 per cent mature polymorphonuclear neutrophiles and 35 per cent young forms. The urine was essentially negative except for a few white blood cells and red blood cells in occasional specimens. The blood non-protein nitrogen was 24 mg. per 100 cc. Blood culture was negative and a throat culture yielded predominantly alpha hemolytic streptococci and a few other mouth organisms. Serologic tests for enteric and heterophile agglutinins and the Hinton test were all negative. X-ray of the chest showed some infiltration in the region of the right middle lobe.

The patient was given routine oral doses of sulfathiazole on entry but did not take them well. He was therefore given 5 Gm. of sodium sulfadiazine intravenously in 1,500 cc. of 0.85 per cent saline followed by 2.5 Gm. in 700 cc. of 5 per cent dextrose in saline twice on the next day. Thereafter, he was maintained on 1 Gm. of sulfadiazine by mouth every four hours throughout his stay. After the second day all medications and feedings were given through a Levine tube. He received a high caloric and high vitamin diet with multiple vitamin supplements. Sulfathiazole ointment was applied to open lesions of the skin. Boric washes and ammoniated mercury ointment were used for the ocular lesions. Dilute sodium peroxide and perborate were used for mouth washes. Codeine with elixir of terpin hydrate was given for the cough and some barbiturates for sedation. The patient was in an oxygen tent throughout the latter part of his stay in the hospital.

After entry numerous vesicles surrounded by areas of erythema appeared in rapid succession on the skin of the neck, upper trunk and upper arms and also on the pharyngeal wall and buccal mucous membranes. Others later appeared on the lower part of the trunk, on the extensor surfaces of all the extremities and also involved the scrotum and urethral meatus. Desquamation of the surface of some of the lesions was present, many of the vesicles became pustular and some became hemorrhagic. Dysphagia increased markedly. The conjunctivae became chemotic, the lids became swollen and vesicles appeared on the lid margins which later became hemorrhagic and encrusted. The number of râles increased in both lungs, more in the dependent areas. There were also patchy areas of dullness and diminished breath sounds which varied in location from time to time. The respirations increased in rate and became more labored; there was increasing cyanosis. There was also considerable sweating. The temperature remained elevated at about 104°F. throughout most of the course except between the fifth and seventh days in the hospital when it ranged between 101 and 102°F. The pulse and respirations also dropped somewhat during this period but during the last two days the temperature, pulse and respirations rose steadily.

The hemoglobin, red and white blood counts all remained essentially the same as at entry. The level of free sulfadiazine in the blood after the intravenous injections was about 10.3 mg. per 100 cc. but dropped gradually to 5.8 on the fifth day and was 28.8 soon after an intravenous dose on the eighth day. A few sulfadiazine crystals were seen in the urine on the fourth day. The blood non-protein nitrogen was 24 mg. per 100 cc. on three occasions but there was a terminal rise to 47. Guaiac tests on the feces were negative on four occasions. An electrocardiogram taken on August 28th showed no abnormalities except for the rapid rate.

Successive sputum cultures showed increasing numbers of hemolytic Staphylococcus aureus in addition to Streptococcus viridans and other mouth organisms in varying numbers. Numerous blood cultures were negative. The complement fixation test for psittacosis was positive (4+) in 1:256 dilution of serum on August 28th, and on September 3rd the serum was



A B

FIG. 1. Case 1. X-rays taken on admission (A) and four days later (B) showing extension of the soft, nodular densities throughout both lung fields.

positive (4+) in 1:256 and 2+ in 1:1024. The latter serum also had a cold agglutinin titer of 1:640. Some of the sputum was fixed and examined histologically and showed chiefly polymorphonuclear leukocytes; no cells with inclusion bodies were seen.

X-ray of the chest on August 31st showed irregular, mottled consolidation of both lower lobes and of the mid-right lung field. Dyspnea and cyanosis increased progressively and breathing became labored after that time. The patient became increasingly disoriented and delirious but there were no abnormal neurologic signs detected and the neck remained supple. He died on September 3rd. A lumbar puncture done shortly before death yielded entirely normal cerebrospinal fluid and the pressure and dynamics were also normal.

The clinical chart, some of the roentgenograms and the skin and ocular lesions in this case are shown in Figures 1 to 3.

Autopsy was performed eighteen hours after death. Over the entire body there were scattered blebs containing clear fluid and varying in diameter from 0.5 to 2.0 cm. There were many dried blebs and many others where the superficial layers were absent, revealing a red-brown, smooth base. Some of the latter were crusted. The eyelids were dark red, ulcerated and encrusted. The conjunctival vessels were congested and there were irregular areas of subconjunctival hemorrhages. The anterior surface of the scrotum and the distal 3 cm. of the skin over the penis were ulcerated and encrusted. There were palpable axillary and inguinal lymph nodes.

There was a very thin layer of fibrinous exudate over both lobes of the left lung and over the lower lobe of the right lung. In addition a small amount of fibrinous, mucoid exudate was present between the base of the left lung and the diaphragm. The combined weight of the lungs was 1,200 Gm. The middle lobe of the right lung was subcrepitant and had a white surface. All of the other lobes were purple-red and showed markedly decreased to absent crepitation. The cut surfaces were dark red-purple and no purulent material could be expressed. There was a miliary nodular appearance, more of the lower lobes, with some dark areas of hemorrhage, congestion and atelectasis, especially of posterior and dependent portions. The mucosa of the bronchi and trachea was congested. The tracheobronchial lymph nodes were not enlarged.

The gastrointestinal tract was normal along its entire length except for slight congestion of the gastric mucosa. The spleen, liver, adrenals, kidneys, ureters and bladder all appeared normal.

The brain weighed 1,760 Gm. The convolutions were slightly flattened. The cerebral veins

were markedly congested. The lateral ventricles and the sulci over the insulae were almost completely obliterated. No gross lesions were seen.

The histologic changes varied greatly in different areas of the lungs. In some the alveoli were essentially normal, in others they contained precipitated albumin and in still others there were fibrin and red blood cells. In many alveoli the lining cells were swollen and vacuolated and a few showed mitotic figures. In such areas the exudate in the alveoli was composed of mononuclear cells, desquamated alveolar lining cells, an occasional multinucleated cell and a rare giant cell of the foreign body type with nuclei up to twenty in number. In addition there were plasma cells in the alveolar exudate. In places the bronchioles contained numerous polymorphonuclear leukocytes and clumps of cocci. There was a marked peribronchial and perivascular infiltration of plasma cells, some lymphocytes, a rare mast cell and eosinophil. In addition there were some large, immature cells of an unidentified type. There was an infiltration in the submucosa of the trachea and about the glands with lymphocytes, many plasma cells and an occasional mast cell.

The spleen was congested and the pulp contained plasma cells in foci and adjacent to the trabeculae. Sections of the liver and kidney showed some plasma cells and lymphocytes in the interstitial tissue. The bladder was congested and its wall infiltrated with lymphocytes, plasma cells, polymorphonuclear leukocytes, eosinophils and mast cells. One acute vascular lesion was noted with fibrin in the wall of the blood vessel. The lymph nodes were infiltrated with immature cells, either lymphoblasts or histioblasts, and some plasma cells and large mononuclears. The testes showed markedly diminished activity, no adult spermatozoa being present. There were few mast cells and lymphocytes in the interstitial tissue. In sections of the bone marrow there were numerous myelocytes, some metamyelocytes and only a few adult polymorphonuclears. The red cells series and the megakaryocytes appeared normal. There were a considerable number of plasma cells present.

There were a few scattered, large mononuclears, lymphocytes and plasma cells in the cerebral meninges. The phrenic nerve showed occasional lymphocytes and plasma cells about the blood vessels in the center of the nerve while the vagus nerve showed no changes. There was a focus of lymphocytes, rare large mononuclears and plasma cells in the posterior lobe of the pituitary adjacent to the pars media.

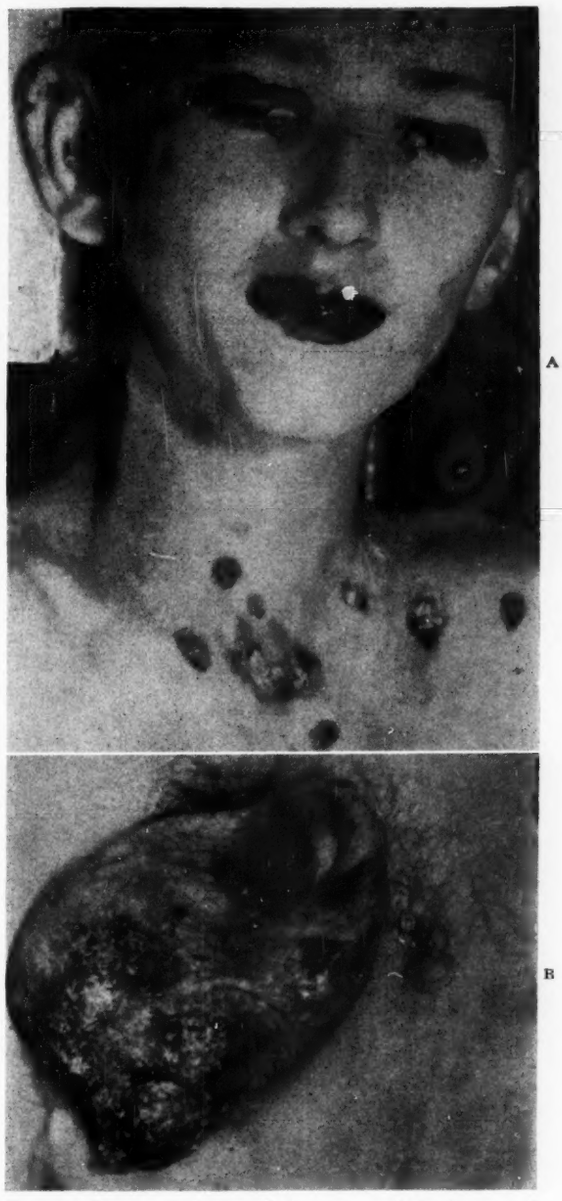



FIG. 2. Case 1. Lesions of the ear, eyelids, lips, neck and upper chest (A); and of the penis and scrotum (B) as they appeared at the time of death.

Sections from the skin showed vesicle formation. The covering epithelium was necrotic. The base of the vesicle consisted in part of intact epithelium and in part of necrotic connective tissue. The content of the vesicle varied. In part it was composed of precipitated albumin and fibrin, in part of polymorphonuclear leukocytes, large mononuclear cells and fibrin and here there were a fair number of diplococci. Some of the hair follicles and coil glands were necrotic.

The necrotic connective tissue was infiltrated with polymorphonuclear leukocytes and large mononuclears. In the deeper portions of the corium there was a perivascular infiltration of large mononuclears, lymphocytes, plasma cells and an occasional eosinophil and mast cell. The blood vessels in the necrotic connective tissue were thrombosed.

Cultures of the heart's blood yielded no growth. Hemolytic Staph. aureus was cultured from the right lower lobe, left lower lobe, pleura and liver, and the latter contained an enterococcus in addition.

Microscopic sections of the skin and lungs are shown in Figures 4A, B and C.

*Comment.* The illness in this patient began with symptoms of an acute upper respiratory tract infection followed by cough and then substernal pain. The first evidence of mucocutaneous manifestations was the sore throat and dysphagia. The bloody sputum may have been the result of irritation and desquamation of the lesions in the mouth. There was obviously a tracheobronchitis but no evidence of involvement of the trachea and bronchi with lesions similar to those of the skin and mucous membranes was found postmortem. It is also of interest that no ulceration of these structures occurred in spite of the increasing number of staphylococci in the sputum and the purulent character of the exudate found in the lumen of the bronchi.

The pulmonary lesion was characteristic of primary atypical pneumonia clinically and roentgenographically. The pathologic findings were consistent with non-bacterial pneumonia in all sections and the only evidence of bacterial infection was in the bronchioles which contained polymorphonuclear leukocytes and clumps of cocci. The mucosa of the bronchioles, however, was intact and their walls were infiltrated with plasma cells. The skin lesion showed only slight evidence of secondary infection, otherwise the mononuclear type of exudate suggested a reaction to a non-bacterial agent. No elementary or inclusion bodies were found in sections of the lungs or of the skin lesion. The brain showed congestion and a negligible cellular reaction of the meninges but was otherwise normal.

There was no history of drug ingestion prior to the onset of the illness or before admission to the hospital, and no personal or family history of allergy was elicited. Although sulfonamides were administered throughout the hospital stay and the pulmonary and mucocutaneous lesions seemed to get worse during that time, it is not possi-

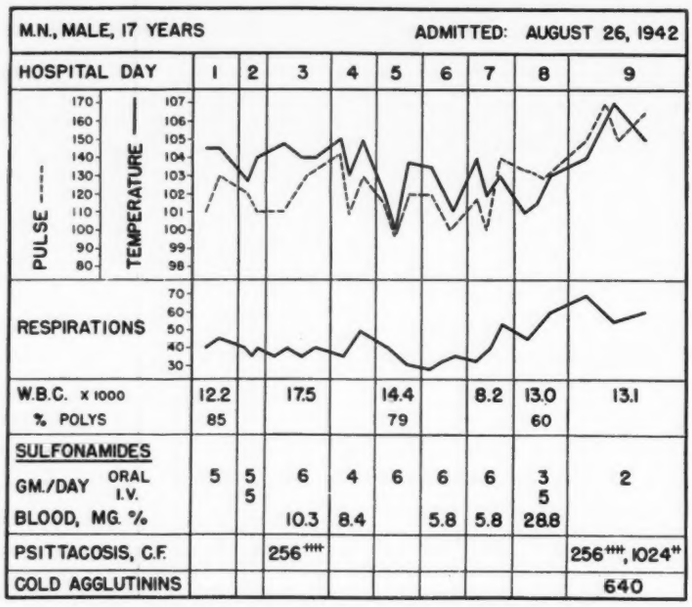
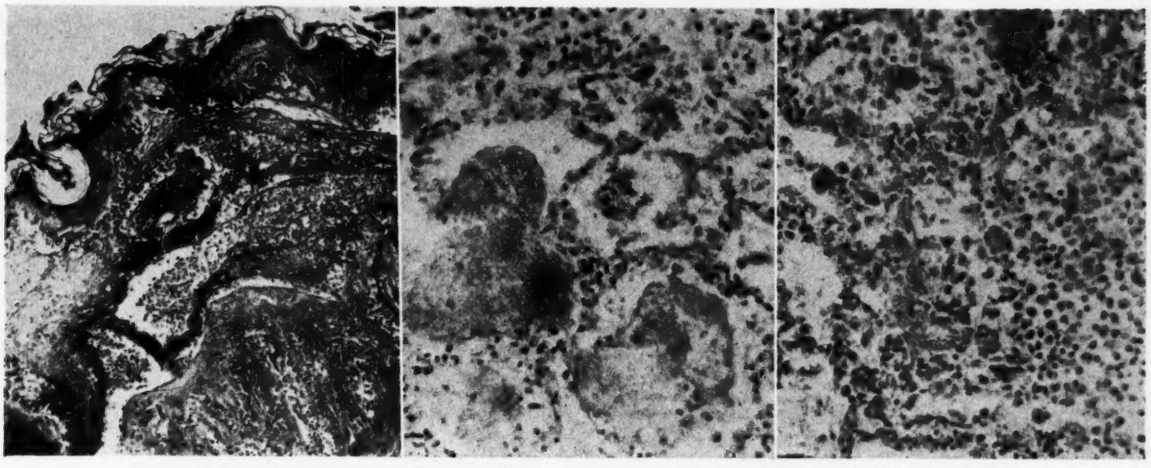



FIG. 3. Clinical chart and some relevant data in Case 1.



A B C

FIG. 4. Case I. A, section through a skin lesion showing vesicle formation with raised epidermis, necrosis of overlying epithelium, exudate of polymorphonuclear leukocytes and fibrin in the necrotic connective tissue and of mononuclear cells in the deeper layers (× 70). B, section from the lung showing alveolar exudate of fibrin and red blood cells (× 125). C, alveolar exudate of mononuclear cells (× 150).

ble in this case to ascribe any of these manifestations to these drugs. On the other hand, the failure of the bacterial infection to advance more than it did either in the lungs or in the skin may be ascribable to the bacteriostatic effect of these drugs.[12] Cases of erythema multiforme bullosum occurring during sulfonamide treatment and ending fatally have been described.[13,14] One case, with every extensive involvement and a severe febrile course but ending in complete recovery, was observed in this hospital. In that case the cutaneous lesions first appeared on the eighth day of treatment with sulfamerazine for pneumonia and the lungs had already cleared at the time.

As to other etiologic possibilities, the only one suggested by the data available is psittacosis. The complement fixation test done with a psittacosis virus was strongly positive on August 28th and September 3rd but no substantial rise was demonstrated. These dates correspond to the sixteenth and twenty-fourth days respectively after the first symptoms of coryza, and the ninth and sixteenth days after the onset of the cough. No definite history of exposure to birds was elicited. Furthermore, the cold agglutinin titer was very high and corresponded to the titers found in other severe cases of primary atypical pneumonia of unknown etiology.[18] Cold agglutinin titers of this magnitude have been demonstrated in other cases of atypical pneumonia from which a virus transmissible to chick embryos, cotton rats and hamsters was isolated,[19] but not in proved cases of psittacosis or ornithosis.[19,20] Attempts to isolate a virus from the sputum, bleb fluid and lungs in this patient were unsuccessful but the methods used were not optimal for that purpose.

CASE II. A twelve-year old girl of Greek descent was admitted to the hospital on September 25, 1942. She had been in good health until six days previously when she developed headache, malaise, nausea and vomiting which continued to the time of admission. Two days later she developed a severe cough and went to bed. On the next day she had two shaking chills after which she developed a sore throat, dysphagia, red and sore eyes, a stuffy nose, substernal pain aggravated by the cough and a fever which rose to 104°F. Two weeks prior to entry she saw a dead pigeon lying on the street, poked it about, then wrapped it up in paper and threw it down the sewer. She had no other known exposure to birds or to persons with rashes or with respiratory infections.

On admission she appeared acutely but not severely ill. Her temperature was 103°F., pulse 120 and respirations 24. The palpebral and scleral conjunctivae were markedly injected, there was a postnasal mucoid discharge, the pharynx was diffusely injected and a few shotty,

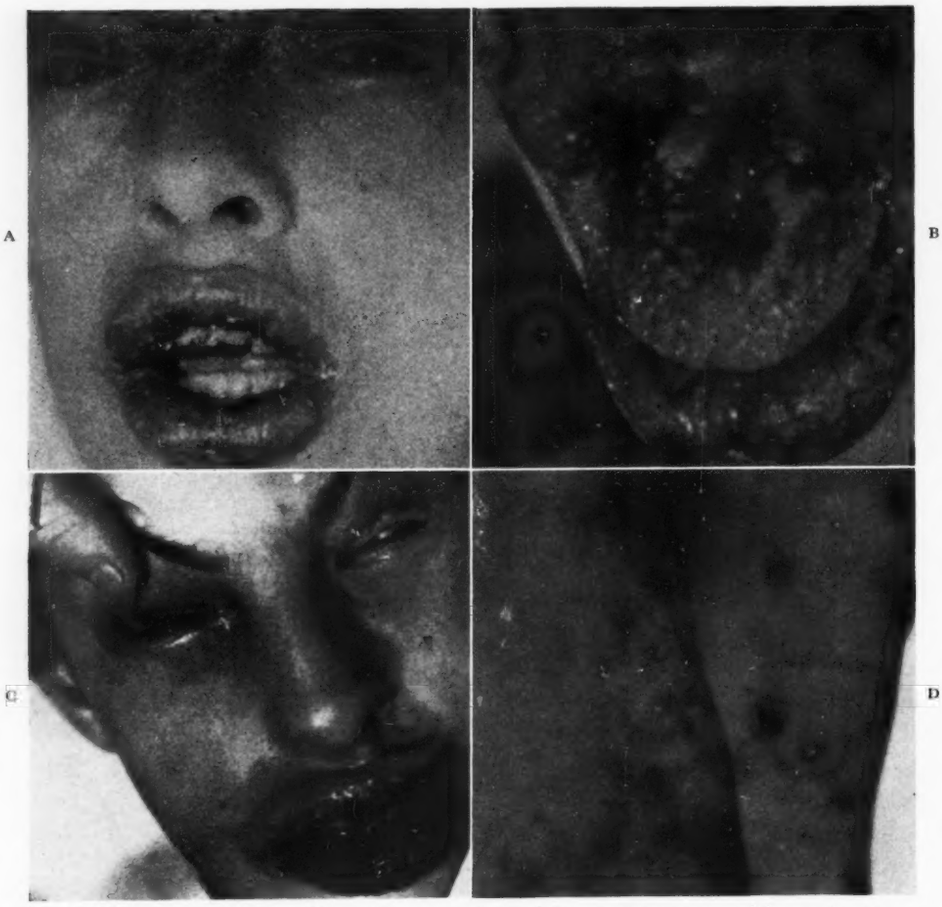



FIG. 5. Case II. Appearance of mouth, eyes and lips (A) and of the tongue (B) on admission; edema of lids and face and hemorrhagic crusts on lips three days later (C); erythematous and vesicular lesions of the lateral trunk and forearm one week later (D).

non-tender cervical lymph nodes were felt. The chest was resonant throughout and only a few scattered musical râles were heard. The rest of the physical examination was negative at this time.

On the following day the patient became markedly prostrated, apathetic and lethargic. Scattered patches of dirty, gray exudate appeared on the soft palate, tongue and uvula, the conjunctivitis had become purulent, fine crepitant râles appeared in both lungs and a rash began to appear on the neck, chest and upper extremities. The skin lesions appeared first as fine maculopapules which rapidly assumed erythema iris forms with central vesicles each surrounded by an inner clear zone and an outer zone of deep erythema. Individual lesions at this time resembled those of chickenpox.

The patient was then put on full adult doses of sulfadiazine by mouth and sulfathiazole ointment was used on the eyes. During the ensuing week the temperature was irregular and ranged between 100° and 105°F., pulse 120 to 150 and respirations 40 to 50. The patient appeared critically ill and was kept in an oxygen tent. The pneumonic process spread to involve all of both lungs with numerous fine and medium crepitant râles but no definite signs of solidification. The ulcerative stomatitis spread to the entire oropharynx which was covered with a pseudodiphtheritic membrane that could be removed with difficulty leaving an underlying bleeding surface. The lips and eyelids became markedly swollen and vesicles appeared at their margins. Vesicular lesions also appeared around the vaginal and anal orifices and became ulcerated. New lesions appeared on the skin over the entire trunk and all of the vesicles became bullous. (Fig. 5.)

Early in the second week the bullous lesions were mostly emptied of their contents leaving hemorrhagic maculopapular lesions and the margins of the lips and eyelids had become encrusted and hemorrhagic. The conjunctivae

had become chemotic and small superficial ulcers developed on the cornea. The pneumonia reached a peak at this time and râles in the lungs then became somewhat fewer. The general condition of the patient improved slightly and the temperature began to drop but then rose again. The sulfadiazine was omitted on October 4th because the possibility of a drug fever was considered but the temperature continued to rise and the patient again became increasingly toxic. She had been given two transfusions during the first week because her hemoglobin was only 10 Gm. per cent and another transfusion at this time produced a severe chill with a rise in temperature to 107°F. Sulfadiazine was given again from October 6th to 10th after which she again improved and the temperature dropped gradually to normal.

The skin began to desquamate during the third week leaving a bright red, scaly surface which left reddish-brown areas of pigmentation after they were healed. The stomatitis had cleared by the end of the third week and the conjunctivitis and keratitis improved steadily and later healed completely without residual. Shotty lymph nodes were felt in the cervical, axillary and inguinal regions and the spleen was felt during the third week. Another bout of fever with daily temperature rises to 101 to 103°F. lasted for two weeks and a third course of sulfadiazine was given for five days during the latter part of this period after which the fever gradually subsided. The lungs cleared progressively until only occasional, fine crepitant râles were heard after the third week.

The blood hemoglobin rose from 10 to 13 Gm. per cent after the transfusions and then again dropped to between 10 and 11.5 Gm. The white blood count was 12,000 on admission with 86 per cent polymorphonuclear neutrophils but dropped to 4,200 on the third day and fluctuated up to 9,250 with 82 to 94 per cent neutrophils. Only occasional eosinophils were seen, not over 1.5 per cent at any time. During sulfadiazine administration the blood concentrations of the free drug ranged between 9 and 14.6 mg. per 100 cc. The blood non-protein nitrogen was normal and the urine examinations were negative except for sulfadiazine crystals and a few leukocytes in the sediment of some specimens. The first x-rays of the chest showed mottled, soft areas of density mostly in the left mid-lung field but subsequent ones on the fifth and eighth hospital days showed nodular

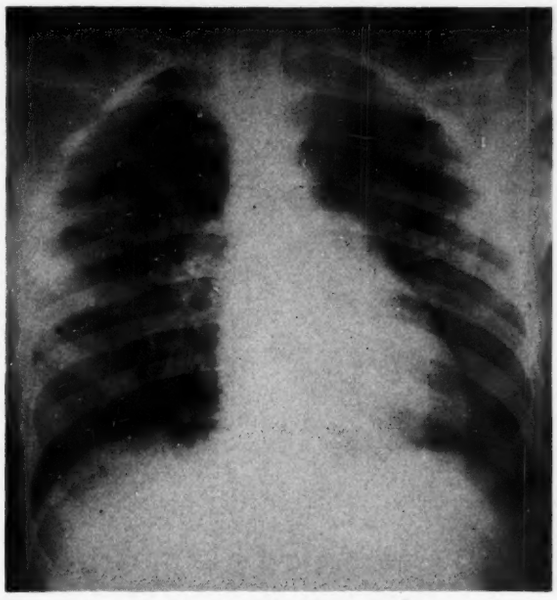


FIG. 6. Case II. X-ray on October 3rd showing nodular densities in both lung fields.

densities throughout both lung fields but these had entirely cleared by the end of the second week. X-ray lesions in the lung are shown in Figure 6.

Smears of the oral and pharyngeal exudate showed a large variety of organisms but repeated cultures yielded predominantly alpha hemolytic streptococci and Staph. aureus in varying numbers. Cultures of the blood and of vesicle fluid showed no growth, those of the conjunctival exudate yielded Bacillus coli and and diphtheroids on some occasions and Staph. aureus on others. The results of studies of the serum for psittacosis and Q fever antibodies and for cold agglutinins are shown with the clinical chart in Figure 7.

*Comment.* The onset in Case II was with rather non-specific manifestations of infection and the first localizing symptoms resulted from the oral and ocular involvement which were followed by appearance of skin and pulmonary lesions. Sulfadiazine was not used until some of these lesions had already appeared and it did not influence their course except insofar as it may have limited the amount of superimposed bacterial infection. The dermatologic picture was characteristic of the more severe type of erythema multiforme exudativum with involvement of the ocular and orificial

surfaces. Clinical and x-ray findings in the lungs were characteristic of the severe and diffuse form of non-bacterial pneumonia with miliary nodular lesions involving most of both lung fields. The recurrent bouts of fever in this patient are not entirely explained. They were not associated with relapses of either the mucocutaneous or the pulmonary lesions and they could not be ascribed to sulfadiazine sensitivity. They may have been due to residual bacterial infection of the skin or lungs.

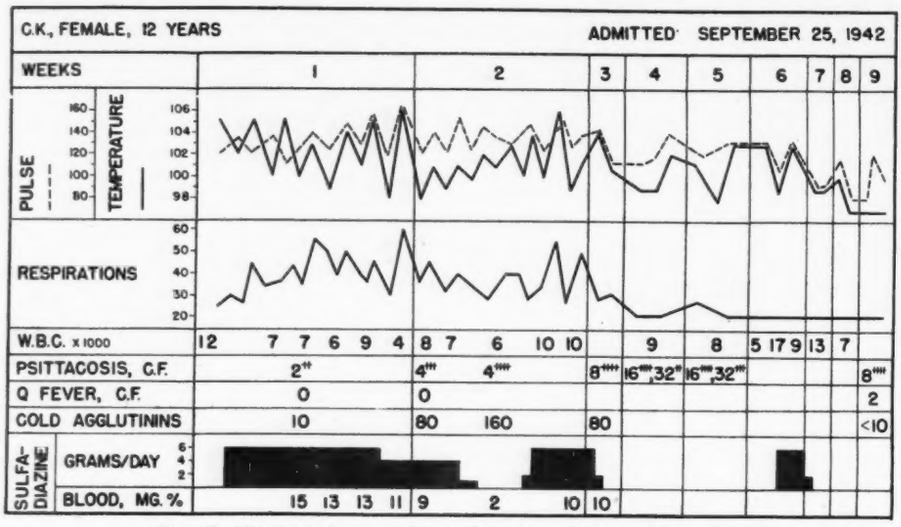
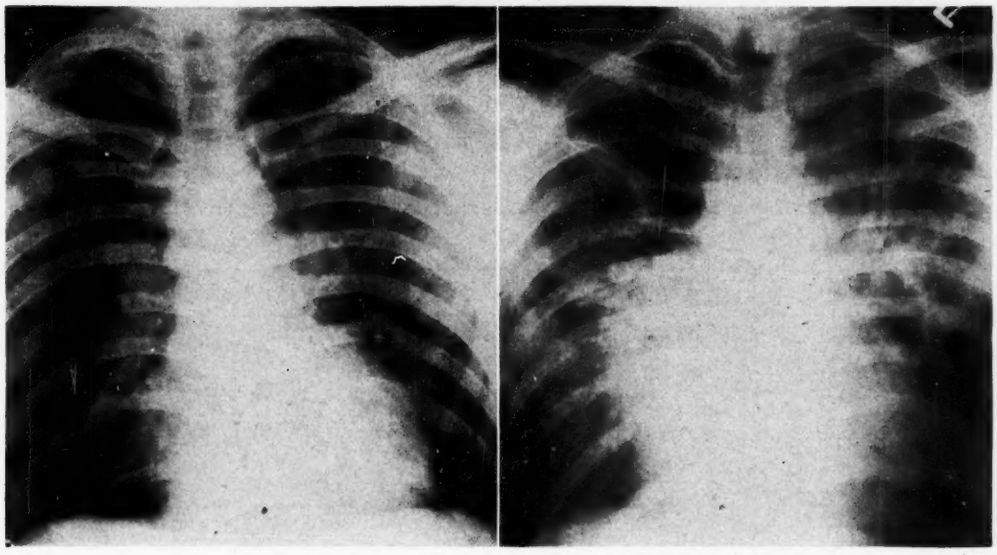



FIG. 7. Clinical chart and certain relevant data in Case II.

This patient was admitted one month after the patient mentioned in Case I and to the same medical service but the two patients came from different parts of the city and had no possible contact with each other. In the first patient, there was a high titer of psittacosis antibodies demonstrated by the complement fixation test during the second (or possibly third) week of the disease but there was no earlier serum available for comparison, no significant rise in titer one week later and no history of exposure to birds could be elicited. In the present case there was a definite history of handling a dead pigeon eight days before the first symptom of any illness and a constant and significant rise in psittacosis antibody was demonstrated in the patient's serum over a period of five weeks followed by a slight fall one month later. There was also a steady and significant rise with subsequent fall in the titer of cold agglutinins. This, too, is of interest in view of the high titer of cold agglutinins later in the disease in Case I.

While no definite evidence was obtained for the presence of a virus in any of the materials studied in these two cases, the methods used and the observations made did not entirely exclude such an occurrence. These two cases, therefore, suggest the possibility of a common or similar etiology in the form of psittacosis or some similar virus but the evidence available is not entirely convincing.

CASE III. A twenty-four-year old, white, American foundry worker was admitted to the Boston City Hospital December 31, 1942. Six days previously he was suddenly taken with a severe shaking chill which was followed immediately by high fever and within a few hours by substernal pain and cough. Two days later he first noticed soreness of the mouth, a sore throat and dysphagia. A physician was called and prescribed a sulfonamide drug in doses of 1 Gm. every four hours on the first day and 0.5 Gm. every hour hours thereafter. On the following day he developed a severe headache, began to have dysuria and his sputum became slightly bloody. Two days before entry his eyes became very sore and sensitive to light. At that time he noticed a rash on his hands and abdomen. All



A B

FIG. 8. Case III. X-rays of the chest on third (A) and seventeenth (B) hospital days.

his symptoms became progressively worse until he was sent to the hospital.

He had suffered from a skin ailment similar to the present one at least three times in the previous ten years but was never as severely ill with the previous attacks. His most recent episode was in 1940 when he was treated at the Peter Bent Brigham Hospital. At that time he gave a history of sensitivity to sea foods, strawberries and tomatoes manifested usually by diffuse erythematous rash. His white blood counts there were 5,000 to 6,000 with 64 per cent polymorphonuclear neutrophils and 5 to 7 per cent eosinophils; no abnormal findings were made out in the lungs. X-rays of the chest showed only slightly increased lung markings; a biopsy of one of the skin vesicles was done and a diagnosis of erythema multiforme was made. He received no sulfonamide drugs at that time.

On entry the patient was acutely ill, uncomfortable but fully oriented. His temperature was 103°F. and he was slightly dyspneic and cyanotic. On the skin of his extremities, trunk and penis there were numerous round and oval pink lesions varying in diameter from 3 mm. to 2 cm. Some of them had vesicular centers. The scleral and papebral conjunctivae were diffusely swollen and injected and there was marked photophobia. The lips and the skin around the nares were also swollen and covered with dried and cracked bloody scabs. The tongue was coated with thick purulent material and the buccal and pharyngeal mucosae were inflamed and tender and covered with dirty, yellowish-gray exudate. There were a few scattered rhonchi and crackling râles throughout the lungs. There were no palpable lymph nodes and no other abnormal physical findings were made out.

The white blood cell count on entry was 12,250 but dropped to 8,400 on the third day and thereafter ranged from 3,100 to 6,200, with polymorphonuclears dropping from 91 to about 80 per cent. The blood hemoglobin was 100 per cent on admission and 85 per cent after the third day. Several urine specimens were all acid and their specific gravity ranged from 1.020 to 1.030; all contained 1+ to 3+ albumin and occasional white blood cells; the first ones had a few and the rest numerous red blood cells in the sediment. Only a trace of sulfonamide was detected in the blood on admission. Successive x-rays of the lungs showed increasing areas of mottled infiltration finally involving both lung fields except the extreme apices. (Fig. 8.) Smears of the sputum showed it to be loaded with polymorphonuclear cells but almost no organisms were seen. Cultures of the sputum at first showed only alpha hemolytic streptococci, but later ones showed increasing numbers of hemolytic Staph. aureus and beta hemolytic streptococci. Several blood cultures were negative. The blood Wassermann and Hinton tests were negative. Complement fixation tests for psittacosis were negative on January 2nd, 11th and 18th.The cold agglutinin titer of the serum was less than 1:4 on January 2nd and 4th, 1:8 on January 11th, 1:32 on January 15th and

finally dropped again to less than 1:4 on January 18th.

The patient was given 5 Gm. of sodium sulfathiazole in saline intravenously at the time of admission but no further sulfonamide therapy was used. Treatment otherwise consisted of frequent sedation, fluids and feedings given parenterally and by mouth with vitamin supplements. Oxygen was given by a tent after the third day. Various types of dressings were applied to the skin lesions without much effect.

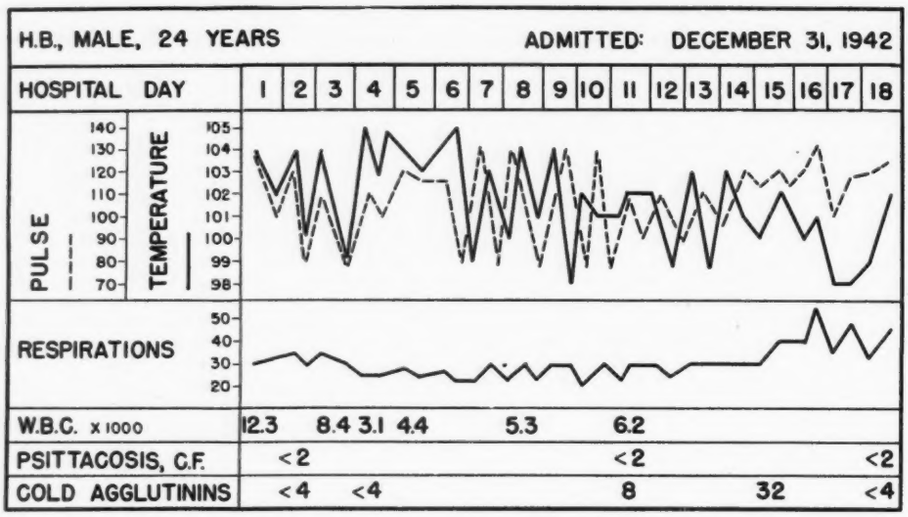



FIG. 9. Clinical chart and certain relevant data in Case III.

The patient's condition continued to get worse during the first few days in the hospital. The skin lesions became frankly bullous in character on the hands and then on the forearms and upper arms. Numerous smaller lesions appeared on the thorax, abdomen, thighs and feet and these also increased in size. Dyspnea and cyanosis likewise increased progressively in spite of oxygen therapy. He became disoriented on the second day and remained so for about a week during which time the signs and symptoms of diffuse pulmonary involvement increased progressively. After the ninth day the patient appeared to improve perceptibly over a period of three or four days. Thereafter, however, the pulse and respiratory rates rose again; dyspnea and disorientation increased; the patient grew steadily more cyanotic and the signs of pulmonary infiltration increased until he died on January 18th. The clinical chart is shown in Figure 9 and the skin lesions in Figure 10.

A biopsy of one of the skin lesions was obtained during the first week. Microscopic sections (Fig. 11) showed a vesicle which contained albuminous precipitate and a few polymorphonuclear cells and fibrin, except in its periphery where the polymorphonuclear cells were particularly numerous. The cells of the inferior surface of the epidermis covering the vesicle were necrotic and were invaded by polynuclear and large mononuclear cells. The base of the vesicle consisted of the connective tissue of the corium and was covered in places by fibrin. This connective tissue showed a perivascular infiltration of lymphocytes and an occasional plasma cell. There was a similar infiltration about the coil glands.

Autopsy was performed fifteen hours after death. There were bullous lesions of different ages, most numerous over the arms and legs and over the shoulders and neck. The most recent were light brown, vesicular, rather well circumscribed and contained thin, colorless fluid. Some of the lesions were dry; others were covered by large crusts. The older lesions were darker in color and somewhat scaly. All measured approximately 1 cm. in diameter. The eyelids were swollen and the conjunctivae were injected. The lips were fissured, hemorrhagic and appeared to have been blistered. The scrotum was covered with confluent, bullous lesions. The glans penis showed a moist, hemorrhagic surface with complete loss of epithelium.

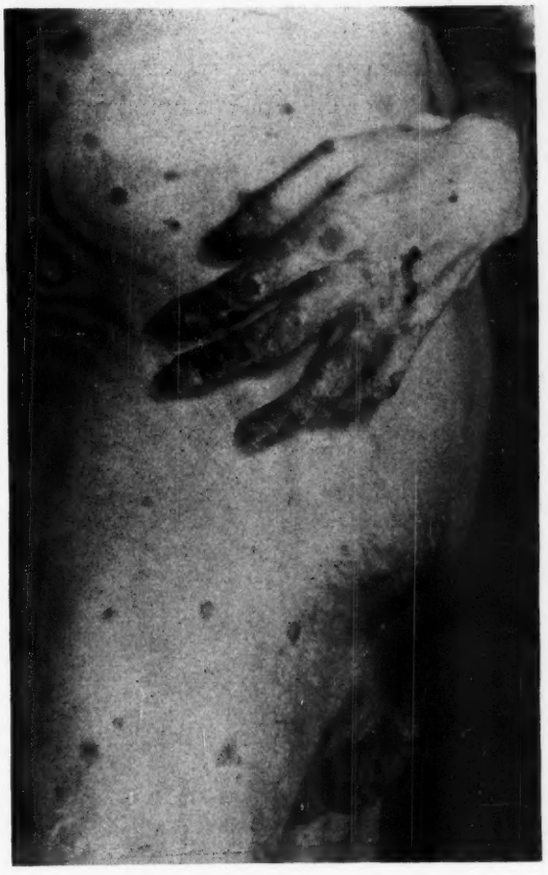
All the pleural surfaces were covered by a thin layer of fresh, yellow, fibrinous exudate most marked over the upper lobes. The left lung weighed 1,145 Gm.; the right, 1,675 Gm. The external surfaces of the lungs were deep blue-red with a hemorrhagic appearance along

the posterior surfaces. The lungs were firm, subcrepitant and in some areas non-crepitant. Upon section the cut surfaces oozed a large amount of blood and appeared nodular. These military nodular areas were slightly raised, yellow-white against a blue to gray-red background. They appeared to be purulent but no pus could be expressed. A small amount of yellow, purulent material could be expressed from some of the smaller bronchioles. The bronchi and trachea were covered with a dark red, slimy exudate containing much blood, and the mucosal surfaces were hemorrhagic. The tracheobronchial lymph nodes were enlarged, measuring 2.5 cm. in diameter.

There was a small amount of red-brown, bloody material in the stomach; the gastrointestinal tract was otherwise entirely negative. The pelvis of the right kidney was red-purple and contained a few drops of thick, yellow purulent material near the inferior calyx which contained similar pus. The ureter of this kidney was slightly dilated but no site of obstruction was found. The left kidney was negative. The bladder was boggy, slightly thickened, contained 50 cc. of clear urine and showed several submucosal hemorrhages. The brain appeared normal.

In sections from the right upper lobe (Figs. 11 and 12) some alveoli contained albuminous precipitate but the majority contained desquamated alveolar lining cells and large mononuclear cells. Other alveoli contained some polymorphonuclear leukocytes, many contained old fibrin in which there were masses of cocci and in some there was hyaline membrane formation. In places the alveolar lining cells were swollen and occasional mitotic figures were present. The bronchioles contained polymorphonuclear and large mononuclear cells and cocci. There was marked peribronchiolar infiltration of plasma cells. The septa showed edema.

In sections from the left upper lobe some alveoli were empty and markedly distended; a few were filled with precipitated albumin but the majority contained an exudate of desquamated alveolar lining cells, many of which were vacuolated. In some alveoli there were also masses of old fibrin, some of which was undergoing organization. The alveolar lining cells were swollen and occasional mitotic figures were seen. An occasional bronchiole was filled with polymorphonuclear leukocytes, large mononuclear cells and cocci. There was a marked

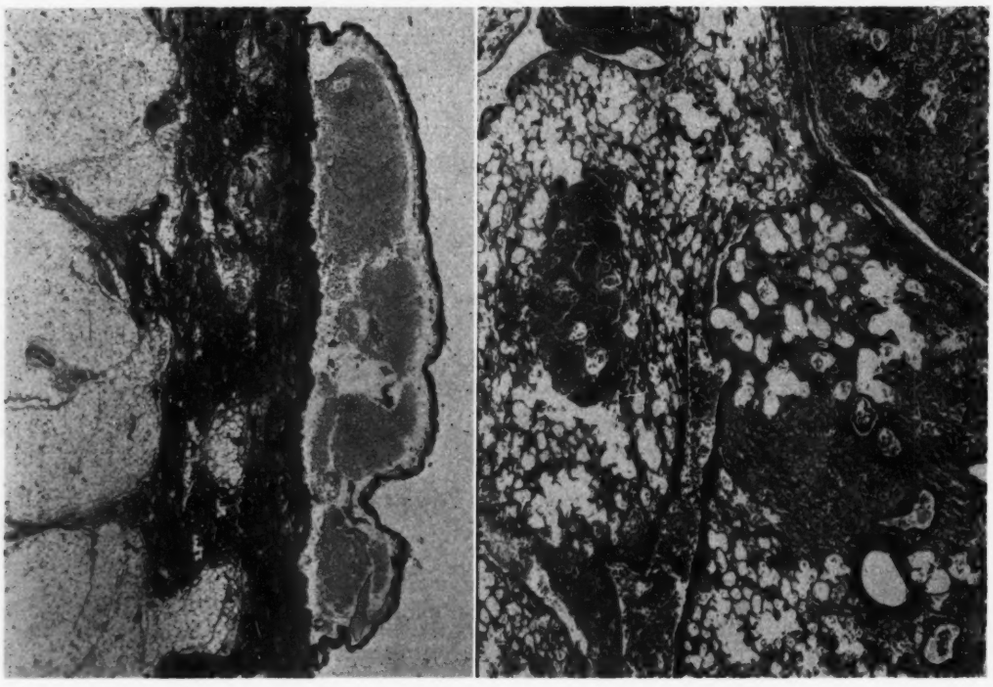


A

B

C

FIG. 10. Case III. Appearance of the lesions on the trunk, hand and penis (A), nose, eyes and lips (B) and feet (C) at the time of death.



A B

FIG. 11. Case III. A, section of skin obtained by biopsy during the first week (× 8). B, section of lung showing patchy distribution of lesions (× 25).

perivascular and peribronchiolar infiltration of plasma cells and also there were many such cells in the alveolar walls and in some places in the alveolar lumens.

Sections from the left lower lobe were essentially similar to those from the left upper lobe, but in one area there was extensive abscess formation with an exudate of polymorphonuclear cells and numerous cocci. Adjacent to this area was a focus of gangrene in which numerous cocci and bacilli were present. One bronchiole had lost its epithelium and its denuded surface was covered with polymorphonuclear leukocytes and fibrin. There was a perivascular and peribronchial infiltration of plasma cells and some lymphocytes. The pleura was covered with a thin layer of fibrin. The trachea was congested and there was an infiltration of the submucosa and around the glands of plasma cells.

There were numerous plasma cells in the pulp of the spleen. The sinuses of a lymph node contained macrophages which were often phagocytic and there was an increased number of plasma cells in the lymph cords. The bone marrow was hyperplastic and evidenced some lack of maturation on the part of the leukocytes.

There was some infiltration of the connective tissues of the kidney pelves with lymphocytes and plasma cells. At this site there was also some fibrin in the blood vessel walls which were infiltrated with a few polymorphonuclear leukocytes.

The cerebral meninges contained a few lymphocytes, large mononuclears and plasma cells.

A culture of the heart's blood was contaminated, but cultures of the left upper lobe and the right upper lobe yielded beta hemolytic streptococcus and hemolytic Staph. aureus.

*Comment.* The illness of the patient in Case III began suddenly with a shaking chill, fever, cough and substernal pain—symptoms characteristic of tracheobronchitis and pneumonia. The sore mouth and throat and the dysphagia began two days later and presumably reflected the development of mucous membrane lesions before that time. The sulfonamide was given only after these symptoms appeared. The skin lesions, the dysuria—which reflected involvement of the urethral meatus—the sore eyes and photophobia all followed. The history of recurrent similar attacks and of erythematous eruptions following ingestion of certain types of food suggest a possible allergic basis for the skin and mucous membrane

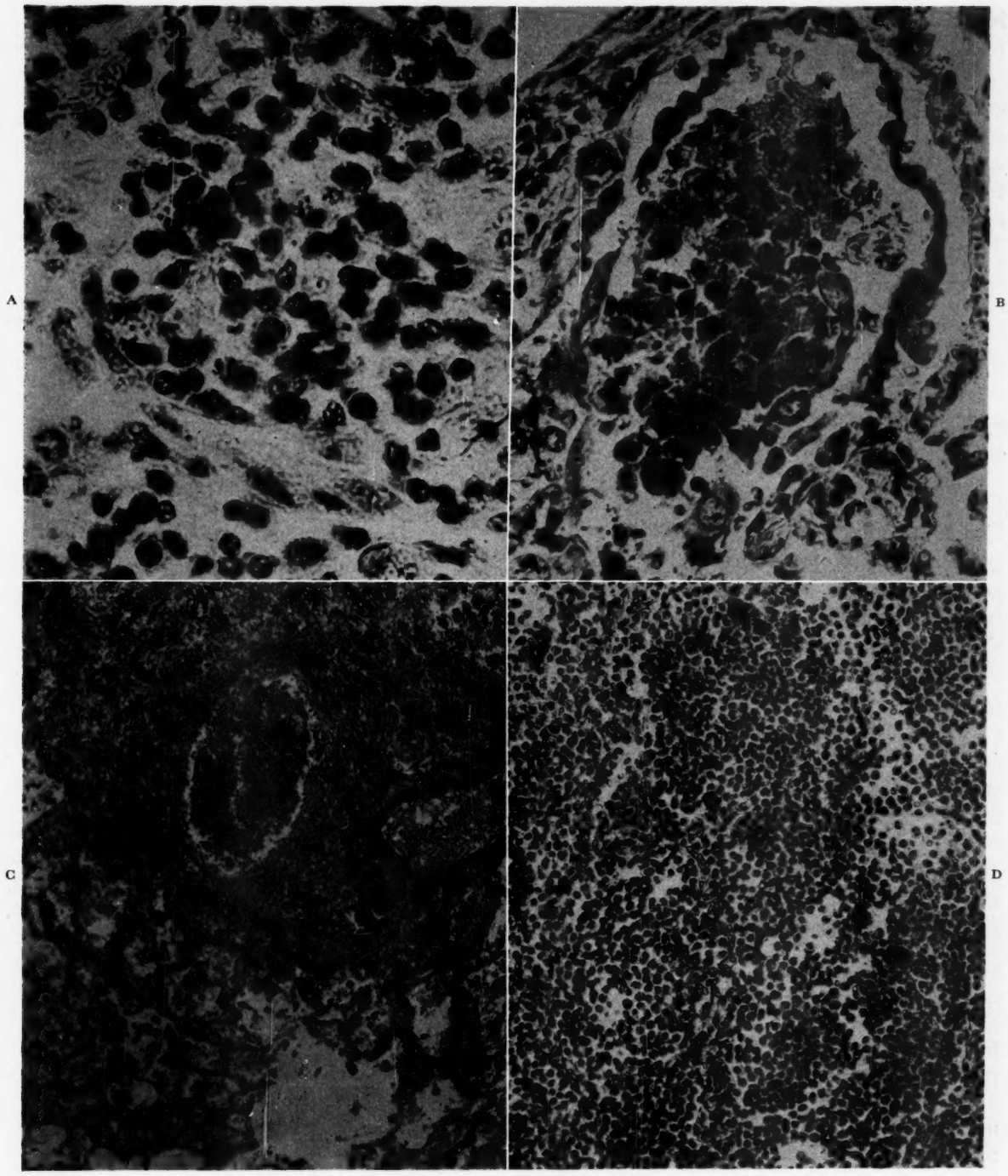



FIG. 12. Microscopic sections of lung showing various types of lesions in Case III. A, interstitial infiltration of alveolar walls with plasma cells (× 425). B, alveolar exudate of mononuclear cells, swelling and proliferation of alveolar lining cells (× 350). C, polymorphonuclear exudate within lumen of bronchiole; mononuclear cells in bronchial walls and in surrounding alveoli (× 100). D, abscess formation with destruction of alveolar walls (× 200).

lesions.* As far as could be ascertained, however, the patient had taken no drugs nor any food to which he was known to be sensitive before the onset of the present episode. Also there was no known exposure to any sick birds or animals or to any infections other than the usual respiratory infections that were prevalent at the time. The exact etiology in this case, as in almost all other similar cases that have been reported, remains obscure.†

In contrast to Case I, in which sulfonamides were given throughout most of the course, these drugs were omitted soon after entry in this patient chiefly because it was thought undesirable to risk the consequences of sensitization. Serious infection with Staph. aureus and Streptococcus hemolyticus occurred and extended down the bronchial tree and into the pulmonary parenchyma. It was manifested by necrosis of some bronchial walls and abscess formation. Such a reaction was not seen in Case I.

The underlying disease in the lungs, however, was similar in both cases and was characteristic of a non-bacterial type of reaction. In this case, as in the previous one, no elementary or inclusion bodies were seen in the sections of the skin, lungs and other tissues, and attempts to isolate a virus from the bullous fluid and from suspensions of the lung by inoculation of mice and embryonated hen's eggs all failed.†

CASE IV. A nine-year old white boy was well until April 17, 1943 when he first complained of mild headache and lassitude. His face appeared flushed at the time, but two days later his temperature was 104°F., he became drowsy and delirious and developed a rash on the face and upper trunk consisting of raised, bright red areas. These gradually extended, became confluent and numerous large blisters appeared on the face, trunk and extremities. His eyelids became swollen at that time. Of interest is the fact that the patient's mother found a dead sparrow in his room on that day and heard him mutter about a bird in his delirium. From his playmates it was later learned that the patient had been nursing the sick sparrow at home in his room for several days and that it had died and he was preparing it for a formal burial just before he became ill. There were no other details of this exposure and none of the playmates were known to have become ill.

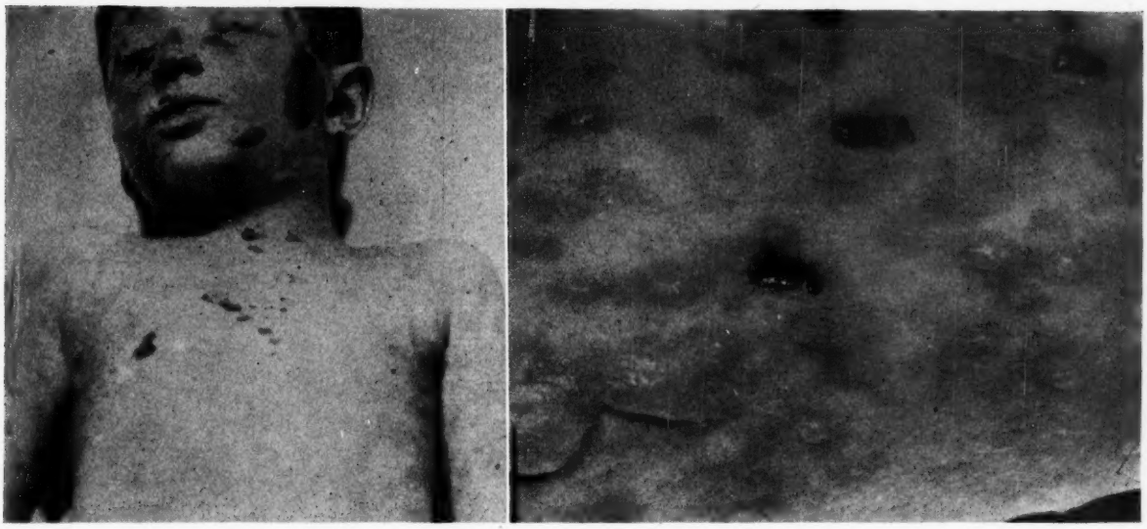
When the patient was admitted to the South Department on April 21st, he appeared extremely ill, semistuporous and breathing with labored and grunting respirations. His eyes were closed by the intense edema of the lids and there was marked conjunctivitis. The pharynx was deeply red, the tonsils enlarged and there were many deep red macular areas on the buccal mucous membrane, some of them with central vesicles or bullae. There was a diffuse morbilliform, non-blanching rash over the body surface, more marked on the upper part of the trunk, with many large bullae within the areas where the maculopapular lesions had become confluent. The epidermis over some of the bullae had been removed in several areas leaving a raw, moist hemorrhagic surface. A few small shotty nodes were felt in the cervical and axillary regions. The lungs were resonant throughout; many coarse rhonchi were heard over the right lung and a few crepitant râles over the left lung but no signs of consolidation were made out. A soft, systolic murmur was heard over the entire precordium. The white blood count was 8,400 with 82 per cent polymorphonuclears. A blood culture yielded no growth.

The patient was given bland local application to the lesions of the skin and mucous membrane, intravenous fluids, nasal oxygen and calcium gluconate for some tremors which were noted soon after admission. Dyspnea and cyanosis increased progressively and the rhonchi became louder and more numerous. The tremors recurred frequently and early on the following morning the patient had a convulsive seizure and died shortly thereafter.

Autopsy was done five hours after death. The lesions of the eyes, skin and mucous membranes were essentially as already described. (Fig. 13.) There were no genital lesions. The pleural surfaces were free, smooth and glistening. The lungs were slightly increased in weight, the

* Of interest in this connection is the recent report of a recurrence of Stevens-Johnson's disease in which some of the symptoms were apparently improved by treatment with benadryl.[21]

† A virus serologically related to herpes was isolated from the lung of this patient after this paper was submitted for publication. The exact relation of this virus to the pulmonary and mucocutaneous lesions is still uncertain.[30]



A B

FIG. 13. Case IV. Lesions of the face and upper trunk (A) and closer view of lesions of upper arm (B) at time of death.

right weighed 225 and the left 200 Gm. They appeared red, hemorrhagic and subcrepitant. Section of the lung revealed hypostasis of the lower lobes and several slightly depressed, dark-red areas 1 to 1.5 cm. in diameter. A frothy exudate could be expressed from the cut surfaces. The rest of the organs appeared normal.

Microscopic sections from all lobes of the lungs showed many normal alveoli and others containing an albuminous precipitate. A few bronchioles contained polymorphonuclear leukocytes and masses of cocci and bacilli. Sections from the right middle and both lower lobes also showed marked congestion and some plasma cells in the alveolar walls. In those from the right lower and left upper lobes there were a few alveoli which showed acute lesions with fibrin and polymorphonuclear cells in the alveolar walls.

A section of a skin vesicle showed its contents to consist of a few polymorphonuclear leukocytes, numerous mononuclear cells with nuclei that were often lobulated and contained heavy chromatin. There was necrosis of all but the superficial layers of the epidermis. The base of the vesicle consisted of connective tissue infiltrated with lymphocytes, macrophages and occasional plasma cells and mast cells. The other organs were essentially normal. A culture of the heart's blood showed no growth.

Tests done on serums obtained on admission and at autopsy were negative for psittacosis antibodies and for cold agglutinins. Inoculation of vesicle fluid and lung suspensions into eggs and mice yielded no recognizable virus.

*Comment.* In this case there was a fulminating bullous type of erythema involving most of the skin, and the mucous membrane of the oropharynx with conjunctivitis but without involvement of the genitals. There were symptoms and signs consistent with pneumonia but autopsy revealed mostly congestion and edema. There was some bronchiolitis and a few, small, scattered, acute alveolar lesions. There was little if any evidence of any interstitial mononuclear reaction and no characteristic involvement of the alveolar walls similar to that seen in Cases I and II. The case is of interest in relation to Cases I and II because of the history of an intimate and prolonged exposure to a sick bird that had died—in this case a sparrow. There was nothing else to suggest psittacosis but the negative serologic findings are not significant because of the short course of the illness, less than five days. The absence of characteristic lesions in the lungs could also conceivably be the result of this fulminating course.

## COMMENTS

The four cases that are reported here all had widespread lesions of the skin and mucous membranes which fit the designation erythema multiforme exudativum. For a discussion of the confused terminology of these and similar dermatologic conditions,

however, the reader is referred to other reports and reviews.[8,11,22] The full evolution of the lesions was seen only in Case II after recovery; they healed completely without scarring but with slight pigmentation. Furthermore, the ocular lesions of the patient in that case also seemed to heal without apparent scarring and without visual impairment in spite of the ulcerations of the cornea that were seen during the acute stage of the disease. The type and evolution of skin lesions and the extent of involvement was otherwise quite similar in each of the first three cases but in Case II they differed in that the lesions advanced more rapidly, were more exudative in character and did not involve the genitals.

The pneumonia in each of the first three cases likewise was similar in character clinically and roentgenographically, except for the terminal increase in the extent and density of the lesions as seen by x-ray in the third patient, which resulted from the superimposed bacterial infection. These pneumonias resembled the severe cases of primary atypical pneumonia with extensive bilateral miliary type of involvement. The findings in Case III, moreover, correspond to those found in a similar case of primary atypical pneumonia complicated by staphylococcal infection.[23]

The gross and microscopic findings in the lungs also corroborated the clinical picture and was characteristic of a nonbacterial type of reaction. There was a patchy miliary type of lesion which consisted histologically of (1) an interstitial infiltration with various kinds of mononuclear cells, predominantly plasma cells, (2) swelling of the alveolar lining cells with occasional mitoses and (3) an alveolar exudate consisting usually of large mononuclear cells and desquamated alveolar living cells but in some areas containing only precipitated albumin and red blood cells.

Lesions containing much fibrin and many polymorphonuclear leukocytes, which are characteristic of an acute bacterial reaction, were rare. They were found in Case III in which there was also some ulceration of the bronchiolar mucous membrane and areas of abscess formation in the parenchyma. In Case I, however, the cellular infiltration of the bronchiolar walls was a mononuclear one, in spite of the presence of a purulent exudate with bacteria in their lumens, and the same was true in most areas of the lungs in Case III.

These findings are also similar in many respects to those described in cases of psittacosis[24–27] except that in the present cases there was less fibrin and red blood cells in the alveoli, the lesions were more discrete and more diffusely scattered throughout the lungs, the interstitial infiltration was more predominant and no inclusion bodies were seen.

There was a striking difference between the rather mild response to secondary infection with staphylococcus in these patients when compared with the severe and extensive type of ulceration and necrosis that occurs under similar conditions in the trachea, bronchi and lungs infected with influenza virus.[28,29] A comparison of the findings in Case I with those in Case III nevertheless suggests that there is some virtue in antibacterial therapy in severe cases in spite of some feeling that, in patients with primary atypical pneumonia at least, there is a relative resistance of the lung to bacterial infection. The use of penicillin in these cases would have been preferable to the sulfonamides because of the predominance of staphylococci and the greater effect of the antibiotic on those organisms. It may be said, however, that while the bacterial infection may have been a determining factor in the fatal outcome in Case III the same was certainly not true in Case I.

The history of exposure to dead birds in Cases II and IV, the high titer of psittacosis antibodies in Case I and the significant rise in titer of such antibodies in Case II are of particular interest. These findings suggest the possibility of infection with a psittacosis-like virus transmitted from birds. Unfortunately, no virus was isolated from materials obtained from these patients. The significance of cold agglutinins in patients with

primary atypical pneumonia is not known but high titers or rises in titers of cold agglutinins have not been reported in proved cases of psittacosis. If Case I and II are indeed cases of psittacosis, then it will be necessary to consider that a cold agglutinin response may occur in some cases of this disease as it often does in cases of primary atypical pneumonia in which psittacosis had been excluded. The unlikely alternative would be to consider that two types of non-bacterial pneumonia coexisted.

There is no evidence to implicate psitacosis in Case III. In that case there was a rise in the titer of cold agglutinins, although not to a high level, and no psittacosis antibodies were demonstrated.* Case IV is included because of the striking skin lesions occurring after what may have been an intimate and prolonged exposure to a sick bird that died. There was no characteristic pneumonia, no virus was isolated and the patient died before any serologic response could be expected.

In connection with these cases some of the skin lesions described by Simpson in cases of psittacosis seen in England[24] are of interest. He observed "rose spots" or similar skin lesions in nine patients, usually between the ninth and thirteenth day of the disease, sometimes in successive crops and always on the trunk. They consisted of small, red maculopapules often surrounded by a white halo with a thin, red line bounding this like a planet. Of other skin lesions sudamina were not uncommon, roseola and erythema occasionally occurred and herpes labialis was present in 5 per cent of his patients.

## SUMMARY

Four cases of erythema multiforme exudativum are reported; three of them were fatal and the autopsy findings are presented.

There was a diffuse miliary type of pneumonia in two of the fatal cases and in the one with recovery. The pneumonia in these patients resembled that of the severe and diffuse type of primary atypical pneumonia of unknown etiology in every respect —clinically, roentgenographically and pathologically; it resembled that of psittacosis in many respects. In one of the fatal instances there was a significant amount of secondary bacterial infection.

Evidence suggesting a possible infection with a psittacosis-like virus was obtained in three cases. In Case I there was a significantly high titer of antibody for psittacosis virus demonstrated by complement fixation. In Case II there was a significant rise in titer of such antibodies during the course of the illness and a history of contact with a dead pigeon eight days before the first symptom. In Case IV there was only a history of contact with a sparrow during its fatal illness. The latter patient died on the fifth day of his disease and the lungs showed only a few acute focal lesions in the alveolar walls. No virus was isolated from any of the patients.

Cold agglutinins were demonstrated in high titer in the serum of the patient in Case I and appeared during the course of the illness in the patients in Cases II and III.

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*Addendum:* Two additional cases of extensive pneumonia and severe erythema multiforme exudativum which resembled Cases I and II clinically were observed recently at the Massachusetts General Hospital through the courtesy of Drs. Greene, FitzHugh and Arlie V. Bock. Neither patient gave a history of exposure to birds. Both recovered and developed high titers of cold agglutinins but no psittacosis antibodies during convalescence.[30]

* A virus serologically related to herpes was isolated from the lung of this patient after this paper was submitted for publication. The exact relation of this virus to the pulmonary and mucocutaneous lesions is still uncertain.[30]

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# Differential Diagnostic Problems in Acute Pulmonary Embolization

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ACUTE pulmonary embolization is a dramatic clinical syndrome of equal interest to both the physician and the surgeon. The disease compels attention for several reasons. Postmortem studies have revealed that a large number of cases escape clinical detection. Clinical experience, on the other hand, has taught that not only is diagnosis and treatment, at times, difficult but that the mortality rate is very high. Pulmonary embolization confounds diagnosis most commonly at the hands of those who are not fully aware of circumstances predisposing to it, or at the hands of those who are not familiar with the diverse clinical syndromes in the guise of which this disease may masquerade.

The following case history is an example of the confusion that may result and the diagnostic difficulties that may ensue in a case of pulmonary embolization.

## CASE REPORT

A forty-nine year old man suffered an acute attack of dyspnea, went into shock and finally collapsed while waiting for his train at a railroad station. An ambulance took him to a hospital of a nearby industrial town. The patient's wife informed the admitting physician that her husband was a "cardiac," having had "angina" which dated to an acute coronary thrombosis three years prior.

On admission, examination revealed dyspnea, fever, leukocytosis and an increased sedimentation rate. Electrocardiographic studies showed auriculoventricular dissociation (the ventricular rate was 65 a minute and the auricular rate 103 a minute); QRS complexes widened to 0.12 seconds and heavily slurred, especially in their terminal portions; deep S waves present in leads I and II; T waves shallow in leads II and III; $R_4$ absent. The pattern was that of a complete auriculoventricular heart block and an atypical right bundle branch block. (Fig. 1 A.)

Diagnosis was recorded as an acute recurrent coronary thrombosis or an acute coronary insufficiency. Treatment consisted of complete bed rest, oxygen and sedatives.

Two and one half weeks after admission, while the patient was still in bed but symptom-free, he had another attack of severe dyspnea and a bout of fever which went up to 103°F. Bedside x-ray at this time revealed pulmonary changes which prompted the diagnosis of an intercurrent bronchopneumonia. Penicillin was administered, the symptoms abated and the "lungs cleared" within a week.

During the fourth week the patient suffered a third acute episode, with his temperature rising to 104°F. Symptoms were predominantly cerebral. Cheyne-Stokes respiration, an aphasia and a transient paralysis of the right side of the body were noted. The diagnosis of a "cerebral accident" was made and the probability of a thrombotic or embolic episode was entertained.

Except for the aphasia, cerebral symptoms gradually cleared. A low-grade fever, however, persisted and toward the end of the fifth week the temperature again rose to 104°F. Purpuric spots appeared at both elbows. At this time the diagnosis of a bacteremia was considered and in spite of repeatedly negative blood cultures intensive penicillin therapy was instituted.

Since diagnosis was doubtful, the therapy of no avail and since a guarded prognosis had been given, the patient's family, in a desperate hope for additional facilities, laboratory studies and medical consultations, insisted that a transfer be

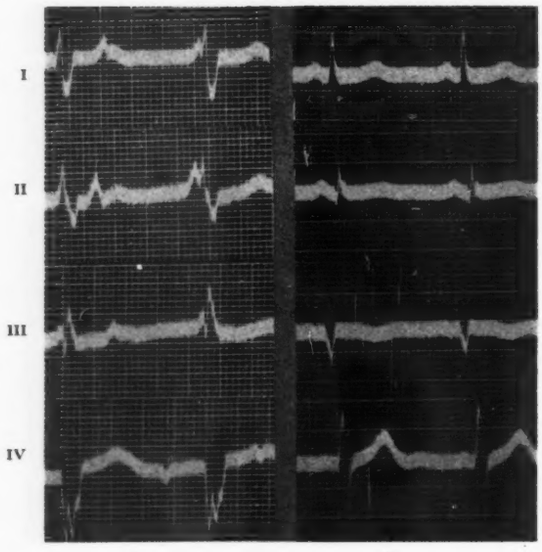


FIG. 1. Electrocardiograms recorded in a patient with an acute pulmonary embolization, who, three years prior had a coronary occlusion with posterior wall infarction. A, tracings taken on day of collapse with pulmonary embolization; B, tracings taken three years prior in the course of convalescence several months after the coronary occlusion.

made to a larger hospital. Accordingly, the patient was transported to a hospital in New York City.

On readmission the patient appeared cachectic, as if he had weathered a protracted siege. He was acutely ill, mentally confused, pale, febrile and dyspneic. The heart action was regular; the rate was 100 to 120 a minute. The systolic blood pressure was low, 85 to 100 mm. Because of the patient's critical condition auscultation of the lungs was difficult. However, signs of pulmonary consolidation were detected in the lower portion of the left lung and upper portion of the right lung, posteriorly. Except for distention, the abdomen was normal. There were extensive purpuric areas over both elbows. A bedside x-ray of the chest showed cardiac enlargement and infiltration of the upper and lower portions of the right lobe and the basal portion of the left lobe. It was not possible to state from the x-ray findings whether the pulmonary processes were due to pneumonia or lung infarctions. A blood count showed 34,000 leukocytes with 92 per cent polymorphonuclears. The cells showed marked toxic granulation. The fever ranged between 102 to 103°F. Respiration was between 40 to 50 a minute. There were evidences of circulatory failure. The patient died forty-eight hours after admission.

The autopsy revealed arteriosclerotic heart disease with hypertrophy and dilatation of both ventricles; an old occlusion with recanalization of the right coronary artery; an old occlusion of the anterior descending branch of the left coronary artery; aneurysmal dilatation of the left ventricle; fibrosis of the interventricular septum and recent occlusion of the left anterior descending and the left circumflex coronaries with a mural thrombus in the left ventricle. Multiple bilateral pulmonary emboli with pulmonary infarctions were found in all lobes.

The cause of death was determined as extensive pulmonary embolization and congestive heart failure.

This unusual case forcibly illustrates how far afield one may be led by a case of pulmonary embolization. Acute coronary thrombosis, bronchopneumonia, cerebral accident and subacute bacterial endocarditis were successively diagnosed in the course of an illness of approximately five weeks' duration.

Autopsy, to be sure, disclosed extensive coronary artery disease with several old occlusions and myocardial fibrosis. There was also a "recent" occlusion of a left coronary artery with a mural thrombus in the left ventricle, which at a glance, might seem to account for the embolic phenomena. This, however, cannot be accepted as a probable cause of the pulmonary lesions in this patient. Emboli from the left side of the heart find their way into the systemic and not into the pulmonary circulation. In view of the fact that pulmonary embolization was extensive, involving all lobes, upper as well as lower, without any significant embolization of other viscera or the extremities, it is reasonable to assume that the heart was not the source of the embolization in this instance and that the source was not revealed by the autopsy.

Pulmonary embolization, of course, is not an uncommon complication of organic heart disease, especially coronary thrombosis. Estimates in this connection vary widely, anywhere from 3 per cent in clinical series to 42 per cent in postmortem series. Many small emboli detected at autopsy undoubtedly produce few, if any, clinically discernible symptoms. Mild symptoms when present are readily obscured by symptoms of heart disease of which pulmonary embolization is a complication. Emboli arising in the left ventricle may lodge anywhere in the systemic circulation. They commonly affect the spleen, kidneys and brain, less often the mesenteric arteries or the vessels of the extremities. In this condition pulmonary emboli are rare, and when they do occur they are but a part of a widespread systemic embolization. With right ventricular thrombi, on the other hand, pulmonary embolization is common. According to Bean[1] as many as 75 per cent of patients in this group have pulmonary emboli.

Bean's observations, based on morphologic studies, no doubt included many cases that were not severe enough to be clinically recognized. This would imply that cardiac emboli are not necessarily productive of massive pulmonary lesions. Bean stated, in fact, that in every one of his patients in whom massive pulmonary embolization had occurred and caused death, the emboli had arisen not from the heart but from distant sources such as veins of the pelvis or lower extremities.

A series of one hundred consecutive cases of coronary occlusion were studied by Nay and Barnes[2] for types of thrombotic and embolic phenomena. Among thirty-seven patients who exhibited such complications, fourteen were diagnosed on clinical criteria as having had pulmonary embolism. It was the direct cause of death in only one patient but it seemingly contributed to the death of five others. Autopsy on these six patients revealed that four had mural thrombi in the right auricle or ventricle. Thrombophlebitis was noted in three of the fourteen cases diagnosed as having pulmonary embolization. Embolization occurred as early as the fifth day in one patient. In all others, it occurred between the sixteenth and thirty-seventh day.

Among surgical patients pulmonary embolization is said to occur in only ½ to 3 per cent of instances.[3] This seemingly low incidence is greatly overshadowed by the incidence encountered among patients with well defined heart diseases. The significance of pulmonary embolization as a surgical complication might be lost if it is not realized that this condition is, nevertheless, responsible for 6 per cent of postoperative deaths.[3,4] Surgical patients are precisely the ones in whom diagnosis is important. Chronic cardiacs carry a certain amount of hazard by virtue of their heart disease. Pulmonary embolization is only one of many serious complications to which they are vulnerable. In surgical patients, on the other hand, in whom the source of the embolization is not a cardiac chamber but more commonly a surgically approachable site amenable to eradication, the diagnosis of pulmonary embolization is all the more important. It may be the only major factor in prognosis.

The detection of pulmonary embolization is at times admittedly difficult. However, there is an immediate lead in the realization that it is a disease of the bedridden, the convalescent and the inactive. In the majority of instances it is due to a thrombophlebitis in some portion of the venous system not associated with the portal circulation. Thrombophlebitis of the deep veins of the lower extremities has been regarded as the most common source. Superficial varicose veins, at times suspected, are perhaps of little importance; in these circulation is retrograde, peripherad and not centrad.

Reporting on eighty-six fatalities among 304 patients with hip fracture, Goladner, Morse and Angrist[5] encountered pulmonary embolization in nine out of twenty-five patients that came to postmortem examination. This constituted 36 per cent of autopsy material and somewhat over 10 per cent of all fatalities. They were impressed with the rôle of the femoral veins as sources of emboli to the point where they advocated prophylactic bilateral ligation in patients who were unlikely to become ambulant at an early date. In contradistinction, Bosworth and his associates, in a series of one hundred patients with trochanteric fractures in whom, because of reduction and the use of Jewett nails minimal bed rest was required, encountered only one patient with pulmonary embolization.[6]

A striking example of the influence of the length of bed rest on the production of pulmonary embolization is presented by Ask-Upmark.[7] In an analysis of 1,454 patients with lobar pneumonia treated in the course of twenty-six years, thromboembolism was observed in only twenty-seven, approximately one out of fifty. More than three-fifths of all cases occurred among persons over forty years of age. They made the interesting observation that with the advent of specific serum therapy during the final four years of their study, more patients with thromboembolism were encountered than during all of the preceding twenty-two years. This they assigned to the survival of patients who otherwise would have succumbed and who, having survived, constituted a large number of added convalescents. An average time of about two weeks elapsed between the onset of pneumonia and thromboembolic phenomena.

Consideration of the pathogenesis of pulmonary embolization yields valuable diagnostic and therapeutic hints. As already stated the source of an embolus may be any portion of the venous system not draining the portal system, thrombophlebitis of the deep veins of the lower extremities being the most common. An embolus dislodged from such a source may locate in any portion of the pulmonary arterial tree and infarction of the lung may result. Often, however, there is no infarction. For the development of an infarct the venous return from the lung it would seem must also be obstructed. Emboli may arrive singly or in showers. Each clinical episode does not necessarily represent a separate embolization. On the other hand, it is not uncommon to find several pulmonary zones of embolization at autopsy in patients who had only a single major clinical episode.

The onset of the clinical picture in some patients with pulmonary embolization may be insidious, or at best, may present but few symptoms. A secondary rise in temperature or an area of lung consolidation without specific bacteriologic findings should always arouse suspicion. Extension of the embolus into larger channels producing massive embolization usually gives rise to major clinical patterns which often simulate other acute diseases and thus create difficulties in diagnosis.

Regardless of the clinical pattern which it may simulate, a major episode of pulmonary embolization is generally ushered in by some measure of vasomotor shock. Fever, dyspnea, rapid thready pulse, low blood pressure, leukocytosis and an increased sedimentation rate are common to all patterns. Leading symptoms may point to diseases such as acute pulmonary, gastrointestinal, cerebrospinal or cardiovascular syndromes. The reason for such divergent and dramatic manifestations is inherent in the mechanism of pulmonary embolization.

As a result of sudden massive obstruction of a portion of the pulmonary arterial tree, for example, respiratory embarrassment usually takes place. This may vary from a simple tachypnea to an agonizing asphyxia.

Cyanosis is often marked. Regional pleuritic pain, its location depending upon the zone of pulmonary involvement, may accompany the dyspnea. The chest pain often radiates to the shoulders or the neck. X-ray of the lungs may show an area of consolidation due to infarction. Such symptoms and findings, together with fever, leukocytosis and increased sedimentation rate, all of which usually accompany the clinical picture, constitute a pleuropheumonic syndrome.

Shock, being a common initial symptom in massive pulmonary embolization, may if protracted produce a cerebral anoxemia to a degree that leading symptoms will point to the brain and not to the lungs. Faintness, for example, may be an early symptom; syncope and convulsions at times follow. If, as usually happens, there is also fever, leukocytosis and an increased sedimentation rate, the clinician for the time being may be hard-pressed to rule out an acute cerebrospinal syndrome.

As a result of shock, marked imbalance of the sympathetic nervous system may take place. Vagus reaction not being adequately opposed may be severe. Acute abdominal pain may be a leading symptom, severe enough at times to suggest an acute visceral crisis. In addition to the abdominal pain, vasomotor shock, fever, leukocytosis and the increased sedimentation rate a mild jaundice may also be present. In acute pulmonary embolization the icteric index is often increased, probably as a result of an acute hepatic anoxia. While such a gastrointestinal syndrome is an uncommon manifestation of an acute pulmonary embolization, it should always be thought of by both the surgeon and the physician.

By far the most common and most dramatic complication of pulmonary embolization is right heart embarrassment. As a result of blocking of a portion of the pulmonary arterial bed there is a rise of pressure within the lesser circulation. This acts as a sudden load on the right ventricle and may produce right heart failure (acute cor pulmonale). If the excessive load persists and if the coronary arteries of the right ventricle are inadequate and cannot supply the functional demands of the overladen heart, the process culminates in an acute coronary insufficiency with myocardial ischemia. Reflex vasospasm of the coronary arteries may contribute to the discrepancy between supply and demand. Postmortem studies of hearts in pulmonary embolization have disclosed extensive areas of myocardial necrosis, especially of the right ventricle and the interventricular septum.[8]

If, as the case often happens to be, symptoms of cardiac embarrassment such as severe chest pain, dyspnea, rapid heart action, fall in blood pressure and vasomotor collapse dominate the clinical picture of pulmonary embolization, a tentative diagnosis of an acute cardiac episode would seem warranted. The fever, leukocytosis and increased sedimentation rate which accompany the episode strengthen the suspicion and not uncommonly the diagnosis of coronary thrombosis is finally made. Electrocardiograms, always resorted to in such instances, at times aid in the differential diagnosis. At other times they are confusing. Depending upon the degree of right heart embarrassment which it produces, massive pulmonary embolization may itself alter the electrocardiogram. In a way its pattern resembles those seen in coronary thrombosis with posterior wall infarction.[9] If such an electrocardiogram is read by one whose experience is limited, the clinical diagnosis of coronary thrombosis may be "confirmed."

The importance of a differential diagnosis between acute pulmonary embolization and coronary thrombosis is at once apparent, if it is realized that timely therapeutic measures such as ligation of deep leg veins and the administration of anticoagulants may

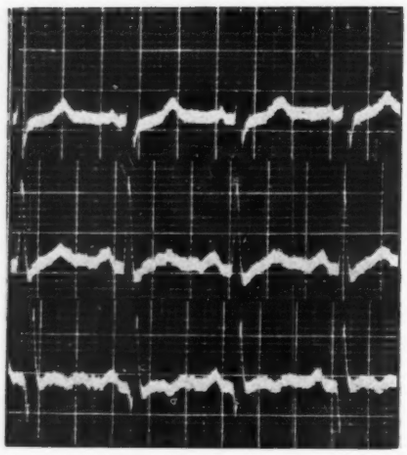


FIG. 2. Electrocardiograms of an "acute cor pulmonale"; standard leads I, II and III taken twelve hours after the onset of an acute pulmonary embolization. (Published by MCGINN and WHITE. *J. A. M. A.*, 104: 1477, 1935. They show: " . . . low origin of the ST interval in lead I and a gradual ascent of the ST interval in lead 2. In lead 3 . . . a Q and a definite and late inversion of the T wave."

arrest further pulmonary embolization. To rest on a diagnosis of coronary thrombosis, on the other hand, when treatment is essentially expectant, is to permit serious mischief to carry on without any attempt to curtail its course.

Differential diagnostic criteria between pulmonary embolization and coronary thrombosis with posterior wall infarction, although at times finely shaded, are nevertheless many. The history, for example, is all important. Pulmonary embolization is essentially a disease of the bedridden or convalescent. Furthermore, this disease does not favor either sex. Coronary thrombosis, on the other hand, generally occurs in patients who have been ambulant and the disease is distinctly more common among males.

The onset of the two diseases is different. In pulmonary embolization the onset is often sudden and overwhelming. In coronary thrombosis it is more gradual and significant prodromas precede the critical state by several hours or days. Chest pain in pulmonary embolization is sharp, pleuritic and has no typical localization. In coronary thrombosis chest pain is pressing or constricting. When severe it is crushing but never sharp or stabbing. Its location is substernal with radiation to the shoulders and arms, especially to the left.

Dyspnea and cyanosis in patients with massive pulmonary embolization are often intense, while in coronary thrombosis they are generally mild or may not be present at all. Shock is frequently a first manifestation of pulmonary embolization. It usually accompanies the chest pain; actually, it precedes it in one case out of three. In coronary thrombosis, on the other hand, shock when present is a culmination of several hours of increasing chest pain. Syncope is not uncommon in pulmonary embolization. It may, in fact, appear as a first manifestation. In coronary thrombosis it is practically never encountered.

Rapid heart action and low blood pressure are early manifestations of pulmonary embolization. They are expressions of vasomotor shock and may accompany or precede the onset of the chest pain. In the early stage of coronary thrombosis, pulse rate, as a rule, is not accelerated and blood pressure is not particularly depressed. The pulse, in fact, may even be slow for several hours after the onset of the chest pain and the blood pressure may rise to unusual heights during the pre-occlusion agony.

Fever, leukocytosis and an increased sedimentation rate appear early in pulmonary embolization and may reach conspicuous heights within several hours. In coronary thrombosis these are late phenomena. They appear twenty-four to thirty-six hours after the onset of major symptoms and, except for the sedimentation rate, seldom reach great heights. An elevated icteric index, common in massive pulmonary embolization, is rarely if ever present in coronary thrombosis.

Chest x-rays, although of little aid during the early stages of pulmonary embolization, may later disclose areas of lung infarction. At times the pulmonary artery may also appear dilated. In coronary thrombosis the x-ray is of limited diagnostic value. The cardiac silhouette is not particularly characteristic. Lung fields may, of course, show passive congestion.

Considerable reliance has been placed in recent years upon the electrocardiogram as a differential diagnostic aid between acute pulmonary embolization and coronary thrombosis. About a decade ago, McGinn and White[10] had called attention to certain features of the electrocardiogram in patients with "acute cor pulmonale." In a study of nine patients with acute cor pulmonale secondary to pulmonary embolization they found significant changes as follows: (1) Prominent S wave and low origin of the T wave in lead I, the S-T segments starting slightly below the base line; (2) a gradual "staircase" ascent of the S-T interval, from the S wave to the T wave in lead II; (3) conspicuous Q waves and a late inversion of the T waves in lead III and (4) in some cases, abnormal direction of the T waves in lead IV without alteration of the QRS complexes. (Fig. 2.) Restoration of the electrocardiograms, they pointed out, may appear in some patients as early as forty-eight hours after the onset. Graphic changes they believed were due to dilatation and partial failure of the chambers on the right side of the heart.

In more recent years, Murnaghan, McGinn and White[11] conducting studies on larger groups corroborated previous observations. They regarded the electrocardiographic changes as an expression of an acute cor pulmonale resulting from the pulmonary embolization. Actually, in some of their patients the diagnosis was first suggested by the electrocardiogram.

An additional electrocardiographic pattern of considerable interest has been pointed out by Durant et al.[12] In a study of three patients in whom electrocardiograms were taken within two to six hours after the onset of acute pulmonary embolization, they noted changes characterized by defective intraventricular conduction. Six to twelve hours after the onset normal intraventricular conduction was reestablished and the electrocardiographic pattern of an acute cor pulmonale supplanted the earlier graph. They, therefore, suggested that graphic changes in pulmonary embolization be viewed as (1) early changes, characterized by intraventricular conduction defect of the atypical right bundle branch type and (2) late changes, characterized by the pattern described by McGinn, White and others as representing acute cor pulmonale. Durant and his associates noted, as have others, that electrocardiographic changes in pulmonary embolization tend to disappear by a gradual restitution toward the normal, except for the persistence in some instances of a $Q_3$ and a negative $T_3$. Figure 3 B represents early electrocardiographic changes in a patient with massive pulmonary embolization.

It should be emphasized, of course, that strictly speaking the pattern of the electrocardiogram never portrays anatomic defects directly, be it pulmonary embolization or any other. The electrocardiogram records physiologic events only. Anatomic defects are diagnosed by deduction from abnormal graphs but particularly from the clinical picture. It should be remembered, furthermore, that electrocardiographic changes in pulmonary embolization are not consistent and that, even when present, they may be altered by stigmas of preexisting heart disease. (Fig. 4.) In this connection warning has also been issued by others. Currans, for example, cautioned that "in appraising the electrocardiographic changes during pulmonary embolization, it should be borne in mind that no one electro-

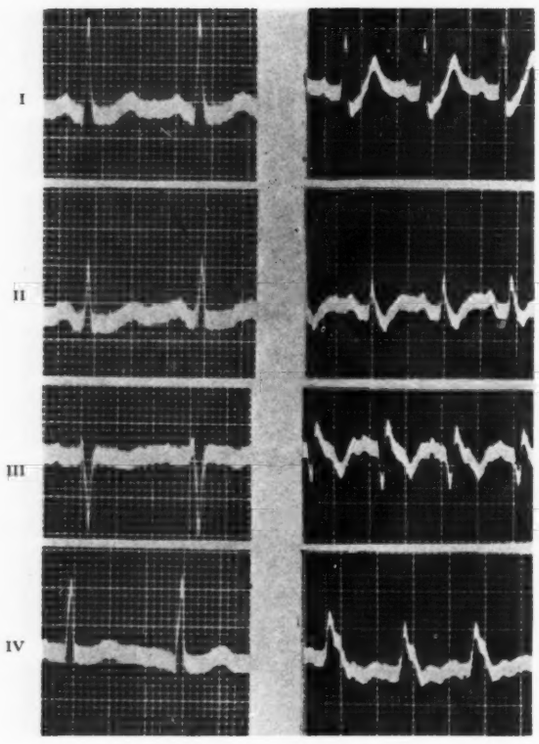


FIG. 3. Electrocardiograms of a fifty-eight year old woman with duodenal ulcer, who two weeks after admission sustained a spontaneous, massive pulmonary embolization. Death occurred within two-and-a-half hours. A, electrocardiograms on admission, essentially normal; B, electrocardiograms taken less than two hours after the onset of the acute episode. They show the "early changes," an atypical right bundle branch block.

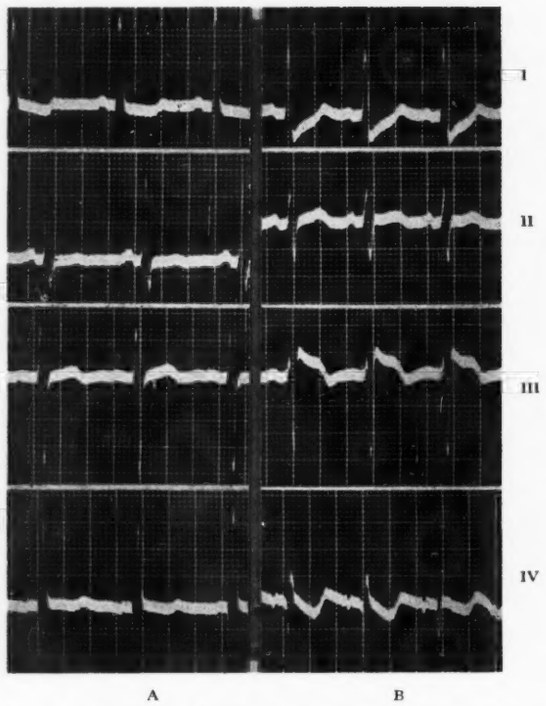


FIG. 4. Electrocardiograms of a seventy-two year old woman with known hypertension, who four days after an abdominal operation developed pulmonary embolization. A, preoperative electrocardiograms showing a pattern commonly encountered in left heart enlargement or left heart "strain." B, electrocardiograms taken twenty-four hours after the onset of pulmonary embolization. The pattern is that of an acute cor pulmonale modified by preexisting heart disease.

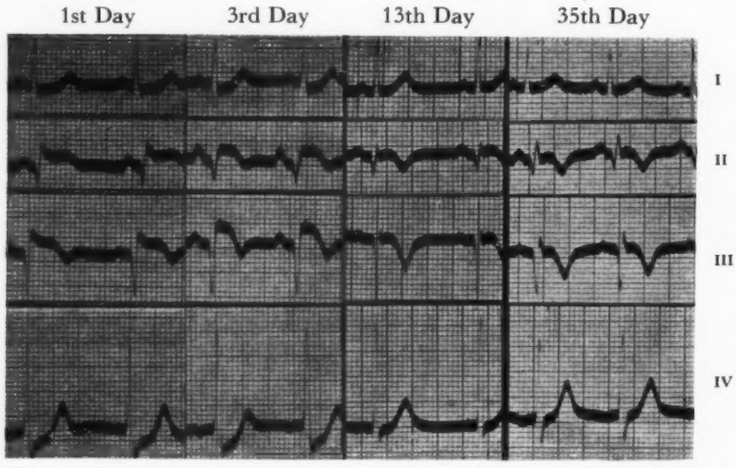


FIG. 5. Electrocardiograms taken consecutively on the first, third, thirteenth and thirty-fifth days in the case of an acute coronary occlusion with posterior wall infarction. The first two tracings (first and third days) represent initial transient patterns, characterized mainly by RST segment deviations. The last two tracings (thirteenth and thirty-fifth days) represent restitution or relatively static patterns, characterized mainly by T wave inversions in leads II and III. Conspicuous $Q_2$ and $Q_3$, present in the earlier graphs persist throughout the restitution patterns of the later graphs.

cardiographic abnormality is consistently present in pulmonary embolization."[13]

In the differential diagnosis between an acute pulmonary embolization and coronary thrombosis the electrocardiogram is of real value nevertheless. An appreciable number of graphs have clearcut features of the pattern described for acute cor pulmonale. Furthermore, even when the pattern lacks convincing features, it differs sufficiently from those seen in acute coronary thrombosis to aid in ruling out the latter condition. For electrocardiographic changes in coronary thrombosis with posterior wall infarction, especially during its early transient stage, are convincing. They are characterized by broad, elevated RST segments and conspicuous Q waves in leads II and III. Corresponding RST depressions may appear in lead I and in chest leads. The T waves in leads II and III are inverted to a varying degree. In the chest leads the T waves are always upright. (Fig. 5.) This early pattern is distinctive and there is little or no danger of ever confusing it with the pattern of an acute cor pulmonale.

Whenever the electrocardiograms of pulmonary embolization and coronary thrombosis with posterior wall infarction do resemble each other, the clinical pictures of the two conditions are, as a rule, strikingly different. It is the partial restitution pattern during a clinically quiescent stage of coronary thrombosis which the electrocardiographic pattern of an acute cor pulmonale may, at times, resemble, but in these cases, too, there are several basic differences in their respective graphs. After the initial RST changes in coronary thrombosis have disappeared, the restitution or "steady" pattern retains a $Q_2$, a $Q_3$ and a deeply inverted $T_3$. As a rule, $T_2$ follows in pattern and is usually also inverted or partly inverted for weeks or months. In the electrocardiogram of an acute cor pulmonale as a result of pulmonary embolization, a large $Q_3$ and a negative $T_3$ are conspicuous features. However, lead II is not similarly

TABLE I

COMPARISON OF CLINICAL FEATURES, LABORATORY AND ELECTROCARDIOGRAPHIC FINDINGS IN ACUTE PULMONARY EMBOLIZATION AND IN CORONARY OCCLUSION WITH POSTERIOR WALL INFARCTION

| | Acute Pulmonary Embolization | Coronary Occlusion with Posterior Wall Infarction |
|---|---|---|
| History | Convalescent (medical or surgical) | History of angina on effort |
| Onset | Sudden and overwhelming | Gradual, hours or even days |
| Pain | Severe, often pleuritic; no typical localization | Pressing or crushing; substernal to shoulder and arm |
| Dyspnea | May be sudden and intense; at times, suffocating | Generally mild; when severe, intensity mounts gradually |
| Cyanosis | May be marked; not relieved by $O_2$ | Usually mild, or not at all |
| Shock | Frequently a first symptom; may precede pain in one-third of patients | When present, it is a culmination of several hours of increasing pain |
| Syncope | May be initial symptom | Rare; may be terminal symptom |
| Pulse | At onset, rapid and thready | At onset, normal or even slow |
| Blood pressure | Generally low (part of shock) | At onset, may be normal or even high |
| Fever | Early; may reach high levels | Twenty-four to thirty-six hours after onset; moderate |
| Leukocytosis | Early; high count | Second or third day; moderate increase |
| Icteric index | Often increased (hepatic anoxemia?) | Not altered |
| X-ray | Pulmonary infarction? | Not characteristic |
| | Dilated pulmonary artery? | Pulmonary congestion? |
| ECG | Early pattern: atypical right bundle branch block | Early pattern: RST rise in leads II and III |
| | Later pattern: large $S_1$, $Q_3$ and negative $T_3$ | Later pattern: $Q_2$, $Q_3$ and negative $T_2$ and $T_3$ |

affected. A well defined Q wave and a negative T wave in lead II are exceptional. Furthermore, a deep S wave in lead I, never present in coronary thrombosis, is a prominent component of the cor pulmonale pattern. In contrasting the two graphs in question one is impressed by the fact that in coronary thrombosis with posterior wall infarction, lead II is a miniature of lead III and that in acute cor pulmonale lead II bears a resemblance to lead I.

In conclusion, one is impelled to reemphasize that electrocardiograms, or for that matter any other single diagnostic aid, should never be permitted to dominate one's judgment in diagnosis. It is the sum total of all facts elicited from the history, physical findings, laboratory and graphic studies that finally determine the diagnosis. It is with this in mind that a differential diagnostic table (Table I) is appended. Within it are tabulated in parallel columns such significant facts in the history and clinical and graphic findings as may, by virtue of some of their striking contrasts, help in the differential diagnosis between acute pulmonary embolization and an acute coronary thrombosis with posterior wall infarction.

SUMMARY

1. Massive pulmonary embolization is a dramatic clinical syndrome of equal interest to physicians and surgeons. Autopsy records disclose that a large number of cases escape detection and clinical experience teaches that among those diagnosed the mortality rate is unusually high.

2. Diagnostic problems are many and are due mainly to the fact that acute pulmonary embolization often simulates other acute clinical syndromes.

3. While pulmonary embolization is more frequently encountered on medical services where a large number of chronic cardiacs are treated, its incidence among surgical patients is equally important. It is among these that early recognition and timely treatment of pulmonary embolization directly determine prognosis.

4. The differential diagnosis between acute pulmonary embolization and coronary thrombosis with posterior wall infarction, being perhaps the most common problem, is discussed in considerable detail, with special attention to electrocardiographic features. A differential diagnostic table is appended.

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# Origin of Thirst in Diabetes Insipidus*†

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DIABETES insipidus, as an outstanding example of polydipsia, offers an opportunity to correlate this extreme type of thirst with our studies on normal man and dog.[2,5,14,24,25] Whether thirst in this disease is primary or whether it is secondary to the polyuria has been discussed for many years. Bellows and Van Wagenen,[1] from a review of the literature and from the results of their own experiments on hypophysectomized dogs with esophageal fistulas, suggest that the polydipsia is the primary functional disturbance.

Yet the successful control of the polyuria and polydipsia of diabetes insipidus by the antidiuretic hormone of the posterior pituitary gland indicates that the polydipsia is secondary to the polyuria. If this is true, the bodily changes in diabetes insipidus should be those of a mild dehydration, the result of the excessive urinary excretion of water. The mechanism of the thirst should then be similar to that observed in dehydration. If this reasoning is correct, untreated diabetes insipidus should be associated with a decrease in plasma volume, extracellular fluid volume and salivary flow similar to that observed in water deprivation.[2,3,4,34,35,36] The alleviation of the thirst by pitressin therapy** should produce increases in plasma volume, extracellular fluid volume and salivary flow similar to that observed when water is ingested by dehydrated individuals.[2,5,34,35,36] Furthermore, the giving of fluids more rapidly than they can be eliminated by the kidney should alleviate the thirst as effectively as pituitrin therapy.

The present studies were undertaken to determine whether: (1) the fluid changes in untreated diabetes insipidus are comparable to those of mild dehydration, (2) the alleviation of thirst by adequate doses of pituitrin alters these changes in the direction of normal hydration, (3) without medication thirst can be alleviated by giving fluid more rapidly than it can be excreted and (4) ingestion of salt induces a thirst response similar to that observed in normal man.

## PROCEDURE

Observations were made on five cases of diabetes insipidus. The patients were studied under the following situations:

Period I. Control period: fluids *ad libitum*.

Period II. Pituitrin therapy: during this period the patients received 1 ampule of pitressin (20 pressor units) subcutaneously every six hours.

Period III. Forcing of fluids: water and liquids were forced until thirst was absent and salivary flow approached the values observed during the period of pitressin therapy.

Period IV. High salt intake: the patient was allowed fluids as desired and given daily 11.0 Gm. of NaCl and 3 Gm. of sodium bicarbonate divided into five equal doses and administered at four-hour intervals from 6 A.M. to 10 P.M.

Each period was of three or four days' duration. The measurements of plasma volume and available fluid were always made on the morning of the third day. Determinations of the hematocrit value and

** The pitressin used in these experiments was furnished us through the courtesy of Parke, Davis & Company.

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† GREGERSEN, M. I. and HOLMES, J. H. Preliminary report. Kongressbericht III des XVI. Internationalein Physiologen-kongresses. Zurich, 1938.

of the concentrations of serum protein, sodium and chloride were made at the time of the plasma volume measurement and also on two earlier occasions during each period of study. However, as the experiments progressed it was impossible to obtain cooperation in every instance so that plasma volume and available fluid measurements were completed in only three patients and salt administered to only one.

During each period twenty-four-hour records were kept of fluid intake and urinary output. Body weight was observed four times daily and more often during periods of rapid shift. The patients were given a standard hospital diet of constant caloric intake and were permitted to add salt to the diet as desired. The amount used was recorded and this figure together with the computed salt content of the diet gave an approximation of the sodium chloride intake.

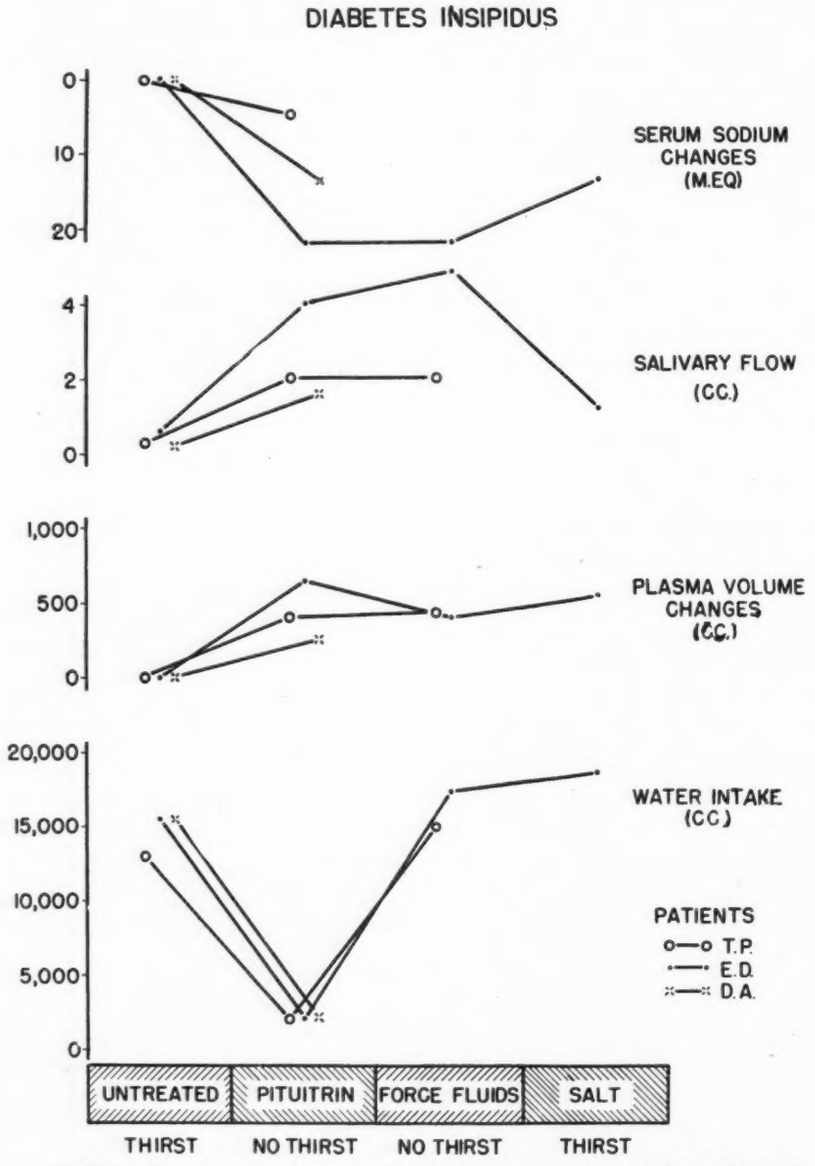


FIG. 1. The effect of various regimens (pitressin therapy, high fluid intake and high salt intake) on serum sodium salivary flow, plasma volume and fluid intake in patients with diabetes insipidus.

The salivary flow was measured during a five-minute period of mouth breathing.[2]

These measurements were made at approximately 9 and 11 A.M. and at 2, 4 and 8 P.M. It was found that there were minor fluctuations in salivary flow throughout the day but that tests taken at the same hour on successive days of the same regimen were remarkably constant.

Following the technic of Gregersen and Stewart,[6] simultaneous measurements were made of the plasma volume by the dye dilution method (T-1824) and of the extracellular volume by the thiocyanate method.[7] All blood samples were taken from the antecubital vein and during the period of sampling the water intake was maintained at the same level as during the previous twenty-four hours. Other blood analyses included determination of the hematocrit value by the Wintrobe tube, of the serum protein by the falling drop[8] or refractometric methods,[9] of the serum chloride[10] and of the serum sodium.[11] Urine samples were analyzed for chloride[12,39] and sodium.[11]

## RESULTS

Figure 1 illustrates the significant changes observed in three cases studied. Without treatment the patients complained continually of thirst, fluid intake was high and there was a significant reduction in salivary flow. Adequate pitressin therapy not only alleviated the thirst but reduced water intake and urinary output to normal values.[14] There were increases in weight, plasma volume and salivary flow.

When pitressin therapy was started on E. D., the body weight increased 3 Kg. within eight hours. There was an immediate reduction in urinary excretion but it was not until four to six hours after starting pitressin that the excessive thirst disappeared and water intake dropped to normal levels. The increase in salivary flow occurred at the time the thirst was alleviated but there was no evidence that the pitressin injections had any specific effect on salivary flow. Peters[13] has reported similar increases in weight after starting pitressin therapy in patients with diabetes insipidus.

The increased salivary flow, plasma volume and body weight observed during pitressin therapy were practically duplicated by simply forcing fluids to the point when thirst disappeared. The intake exceeded the output. The retention of fluid was comparable to that observed during pitressin therapy. The patient, E. D., testified that the forcing of fluid dispelled the thirst as effectively as did pitressin therapy. Furthermore, his appetite was improved and he lost the lethargic feeling of which he complained during the control period.

TABLE I
OBSERVATIONS IN CASE E.D.

| | Period I (Control) | Period II (Pitressin) | Period III (Forced Fluid) | Period IV (Salt) |
|---|---|---|---|---|
| Water intake (L.) | ..... | 3.1 | 17.3 | 18.7 |
| Urine output (L.) | 15.6 | 2.6 | 15.6 | 17.7 |
| Weight (Kg.) | 60.8 | 62.0 | 62.7 | 62.3 |
| Salivary flow (cc./5 min.) | 0.6 | 4.0 | 4.9 | 1.2 |
| Plasma volume (cc.) | 2,440.0 | 3,070.0 | 2,800.0 | 2,980.0 |
| "Available fluid" (L.) | 13.8 | 14.8 | 16.8 | 16.9 |
| Serum proteins (Gm. %) | 7.5 | 6.5 | 6.2 | 5.7 |
| Serum sodium (mEq./L.) | 155.0 | 133.7 | 133.1 | 141.7 |
| Urine NaCl (Gm./24 hr.)* | 9.5 | 11.1 | 6.4 | 23.2 |

* Represent average for each four-day period.

The beneficial effects of the forcing of fluids are further confirmed by the fact that E. D. voluntarily followed a regimen of this type after stopping pitressin therapy because of the inconvenience of administering subcutaneous injections. On awakening in the morning he is very thirsty and during the next thirty minutes drinks 2 to 3 liters of fluid. He repeats this procedure several times during the day. As a result his thirst is alleviated and salivary flow increases. While E. D. was on this regimen, observations were made several times of the changes in salivary flow, the body weight, the concentrations of serum sodium and serum proteins and the hematocrit value. The results of one day's observations are presented in Table II. In the morning, before taking water, his weight was 65.5 Kg. Two hours after drinking water his weight was 68.3 Kg. and remained at this higher level until bedtime. The reduction in concentration of serum proteins and serum sodium represent a 5 to 10 per cent increase in plasma and

extracellular fluid volume respectively. A comparison of Table II with Figure 1 shows that E. D. repeats every day the situations existing in periods I and III. These changes are consistent with those observed when a normal dehydrated person restores his water deficit.[2,36]

TABLE II
CHANGES IN WEIGHT, SALIVARY FLOW, SERUM PROTEINS AND SERUM SODIUM WHEN THE PATIENT (E. D.) WAS IN A DEHYDRATED STATE ON ARISING IN THE MORNING AND AFTER THE THIRST WAS ABOLISHED BY INGESTION OF 3 LITERS OF WATER

| | Weight Kg. | Salivary Flow cc./5 min. | Plasma Proteins Gm. % | Serum Na+ mEq./L. | Thirst |
|---|---|---|---|---|---|
| A.M. before drinking | 65.5 | 0.1 | 7.75 | 146 | Marked |
| 2 hr. after water (3 L.) | 67.3 | 2.0 | 7.1 | 138 | None |
| 5 P.M. | 67.6 | 2.8 | 6.9 | 138.8 | None, slight |

In the case of E. D. salt was given as a means of increasing the plasma and extracellular volumes to values comparable with those observed during the periods of pitressin therapy or when fluids were forced. The giving of salt caused intense thirst and a reduction of salivary flow similar to that seen during the control period. There was an increase in water intake and urine output similar to that reported by other investigators.[13,15,16,17] After an initial period of salt retention urinary excretion of chloride equalled the NaCl intake. The serum sodium concentration fluctuated between 141 and 145 Meq. per liter. (Table I.)

The changes in salivary flow for the five cases are tabulated in Table III. These measurements were made at the time of the blood volume studies and show that the salivary flow was consistently reduced in untreated diabetes insipidus at a time when the thirst was intense. During the periods of pitressin therapy and the forcing of fluids thirst was alleviated and the salivary flow rose. For comparison five normal subjects were tested for a two to three-week period and the values for salivary flow in the normal subject were found to be similar to those in the patients only during the periods of pitressin therapy or of the forcing of fluids. In two of these subjects the forcing of fluids up to 12 to 16 liters per day did not produce any increase in salivary flow.

The values for serum sodium concentration are presented in Table IV. These were determined on blood samples taken at the time the plasma volume measurements were made. Many other sodium determinations were done in these patients and served to amplify and support the results shown in Table IV. The highest serum sodium values are noted in Period I (water *ad libitum*) and in the case of E. D. are well above normal values for man.[32] In every instance there was a drop in concentration of serum sodium both during the period of pitressin therapy (Period II) and when fluids were forced (Period III). Serum chlorides were done in three patients and the changes observed were similar to those noted for serum sodium.

TABLE III
CHANGES IN SALIVARY FLOW (EXPRESSED AS CC. PER FIVE-MINUTE PERIOD) IN FIVE CASES OF DIABETES INSIPIDUS. THIRST WAS SEVERE IN PERIODS I AND IV AND ABSENT IN PERIODS II AND III

| Patient | Period I (Untreated) | Period II (Pitressin) | Period III (Forced Fluids) | Period IV (Salt) |
|---|---|---|---|---|
| | cc./5 min. | cc./5 min. | cc./5 min. | cc./5 min. |
| E. D. | 0.6 | 4.0 | 4.9 | 1.2 |
| T. P. | 0.3 | 2.0 | 2.0 | |
| S. D. | 0.2 | 2.6 | 1.0 | |
| L. | 0.2 | 2.8 | 1.2 | |
| D. A. | 0.2 | 1.6 | | |

When values for the extracellular volumes were calculated from the variations in concentration of serum sodium or chloride, the changes were always in the same direction but occasionally not as large as the corresponding change measured by the thiocyante. Although it was not possible to carry out accurate balance studies in these patients, it is presumed that this difference could be accounted for by urinary excretion of sodium and chloride. The extracellular volumes observed for E. D. shown in Table I

were higher in the periods of pitressin therapy (II) and of the forcing of fluids (III) than in the control period (I). Similar changes were noted in the other patients.

Determinations of plasma protein concentration and hematocrit values were made

TABLE IV

VALUES FOR SERUM SODIUM IN FIVE CASES OF DIABETES INSIPIDUS SHOWING THE CHANGES WHICH OCCUR WITH PITRESSIN THERAPY, FORCING OF FLUIDS OR ADMINISTRATION OF SALT

| Patient | Period I (Untreated) | Period II (Pitressin) | Period III (Forced Fluids) | Period IV (Salt) |
|---|---|---|---|---|
| | mEq./L. | mEq./L. | mEq./L. | mEq./L. |
| E. D. | 155 | 133.7 | 133.1 | 141.7 |
| T. P. | 142.5 | 137.2 | | |
| S. D. | 143 | 137 | 136 | |
| L. | 146.5 | 141.3 | 141.0 | |
| D. A.* | 137.2 | 123.6 | | |

* This patient also had adrenal insufficiency which accounts for the low values of serum sodium.

frequently in these patients to obtain additional information on the plasma volume changes. It can be seen in Table V that the serum protein concentrations were high during untreated diabetes insipidus and decreased when the fluids were forced or pitressin therapy was given. In untreated diabetes insipidus patients there were considerable fluctuations in the values, related apparently to temporary changes in water balance.*

* Dr. J. I. Nurnberger of the Neurological Institute, College of Physicians and Surgeons, Columbia University, observed recently in another case of diabetes insipidus the changes in fluid balance produced by pituitary injections. We made measurements of salivary flow in this same patient. Unfortunately, these measurements were not made on the same period of pituitrin therapy, but since the weight changes indicated approximately the same degree of hydration the data have been combined for comparison with the other five patients. Following pituitrin, the patient gained 3.2 Kg., the plasma volume increased from 2,640 to 2,940 cc., the plasma protein decreased from 7.2 to 5.6 Gm. per cent and the hematocrit value from 50.6 to 44.9. The salivary flow increased from 0.2 to 2.0 cc. per five-minute period. The injection completely alleviated the thirst and the urinary output dropped from approximately 6,000 to 900 cc. a day. The measurements in this patient confirm our earlier observations.

## COMMENTS

The experimental evidence in the five cases of diabetes insipidus studied appears to support our hypothesis that the thirst and fluid changes in untreated diabetes insipidus are similar to those of mild dehydration. It was shown, furthermore, that pitressin therapy or the forcing of sufficient fluids to relieve thirst produces changes similar to those observed when water was given to normal dehydrated subjects.[2,36] During these periods there were increases in salivary flow, in body weight, in plasma and extracellular volumes and decreases in hematocrit values and in concentrations of serum proteins, sodium and chloride. These changes are identical with those observed in dehydrated dogs[5] or men after ingestion of water.[2,34,35,36] Pitressin does not appear to exert any specific effect other than through its antidiuretic action since the same changes can be produced by the forcing of fluids. Salivary flow and thirst in diabetes insipidus can therefore be explained by Cannon's theory of thirst.[14,37]

TABLE V

VALUES FOR PLASMA PROTEINS IN FIVE CASES OF DIABETES INSIPIDUS SHOWING THE CHANGES WHICH OCCUR WITH PITRESSIN THERAPY, FORCING OF FLUIDS OR ADMINISTRATION OF SALT

| Patient | Period I (Untreated) | Period II (Pitressin) | Period III (Forced Fluids) | Period IV (Salt) |
|---|---|---|---|---|
| | Gm. % | Gm. % | Gm. % | Gm. % |
| E. D. | 7.5 | 6.5 | 6.2 | 5.7 |
| T. P. | 6.8 | 6.0 | 5.6 | |
| S. D. | 8.2 | 7.7 | 7.6 | |
| L. | 7.6 | 6.8 | 7.0 | |
| D. A. | 5.9 | 5.5 | | |

Gregersen[14,38] suggests that the mechanism of the decrease in salivary flow in dehydration can be explained by a reduction in blood flow to the glands, and he demonstrated parallel reductions in salivary flow and plasma volume in dehydration produced by water deprivation and sweating. Parallel reductions in plasma volume and salivary flow were likewise found in our

patients in the untreated state when compared with the situation existing after pitressin therapy or the forcing of fluids. Furthermore, the presence in these patients of normal values for salivary flow only during the periods of pitressin therapy or forcing of fluids, and the observation that in normal hydration the forcing of fluids does not increase salivary flow suggest that the thirst mechanism and salivary flow changes of untreated diabetes insidipus are identical with those in dehydration.

There is evidence in the literature to support these observations. Findley and White[23] likewise found that thirst was alleviated in a case of diabetes insipidus in which fluids were forced to increase the polyuria. Also the observations by others on the effects of pitressin therapy on plasma volume[18,19] and on serum concentrations of protein,[13] sodium and chloride[13,20] are similar to those shown in Tables I, IV and V. That the thirst of diabetes insipidus is a result of polyuria was shown in experiments on rats by Richter and Eckert[26] and by Swann.[27] These authors found that when the polyuria was controlled by ligation of the ureters thirst was absent. Furthermore, water deprivation in diabetes insipidus produces more marked signs of dehydration after twenty-four to forty-eight hours[21,22] than are observed in the normal animal after eleven days of water deprivation.[14]

Other investigators have observed that the administration of salt in diabetes insipidus intensifies the thirst and increases the polyuria.[13,15,16] When salt was given to E. D., the increase in plasma and extracellular volumes (NaScN) were similar to or greater than those observed with pitressin therapy or the forcing of fluids. The thirst exhibited by E. D. following salt was also found in normal men when salt was administered by mouth or by intravenous injection of hypertonic salt solution.[24,33] Normal men likewise exhibited an increase above the normal in plasma and extracellular volume and a decrease in salivary flow. This suggests that the thirst mechanism in diabetes insipidus responds in a normal manner to the ingestion of salt. However, the magnitude of the thirst response provoked by ingestion of salt is much greater than in the normal because of the dehydration. This is in keeping with our observations that in the dog the giving of hypertonic salt solution in dehydration will evoke a much greater drinking response than would have been predicted from the sum of the drinking responses previously observed in either situation alone.[5]

At the high rate of fluid exchange that exists in diabetes insipidus frequent shifts in the fluid balance apparently occur. This is indicated by the marked variations in serum concentration of protein, sodium and chloride both in the untreated state or when starting pitressin therapy. If the patient abstains from drinking for a few hours, there will be a marked increase in concentration of serum sodium, chloride and proteins. In the case of D. A. after five hours of water deprivation the body weight decreased 4 per cent and at this time the serum protein concentration had increased 8.6 per cent, the serum sodium 8 per cent and the serum chloride 9.7 per cent. Similar changes in concentrations of serum sodium, chloride and protein have been reported by other investigators[13] and some have even attached diagnostic significance to the variations.[28] Our measurements of plasma volume and extracellular volume reveal that the changes in serum concentrations of protein, sodium and chloride are in a large part merely a reflection of the changes in volume of the fluid compartments.

In the case of E. D. there appeared to be a slight increase in total twenty-four-hour chloride excretion when he was given pitressin therapy and a decrease when fluids were forced. (Table I.) However, the serum sodium changes showed a marked variation from patient to patient (Table V) and when correlated with extracellular volume changes (NaSCN) suggested a considerable variation in sodium and chloride excretion in the several test periods. This is in agreement with reports from the literature which indicate that in diabetes insipidus following

administration of pituitrin the urinary excretion of chloride may either increase,[29] decrease[20] or remain unchanged.[31]

## CONCLUSIONS

Five cases of diabetes insipidus were studied to evaluate the mechanism of the polydipsia under the following situations: (1) water *ad libitum*, (2) pitressin therapy, (3) the forcing of fluids and (4) ingestion of salt (one case).

During the periods of intense thirst there was always a reduction of salivary flow. When thirst was abolished by pitressin therapy or by the forcing of fluids, the salivary flow increased to normal values. (Table III). These observations are consistent with the "dry mouth" theory of thirst.

Pitressin therapy or the forcing of fluids resulted in an increase in plasma volume and extracellular volume (NaSCN) over the values observed for untreated diabetes insipidus. (Fig. 1, Table I.) There were corresponding reductions in serum concentrations of protein, sodium and chloride. (Table IV and V).

It is suggested that the thirst mechanism in diabetes insipidus is similar to that observed in simple dehydration and is caused, in this instance, by the severe polyuria. This is confirmed by our observations that pitressin therapy or the forcing of fluids alleviate thirst and produce increases in plasma and extracellular volume and in salivary flow similar to that observed after ingestion of water in dehydration.

It is pointed out that the wide fluctuations of serum protein, sodium and chloride concentration are probably a reflection of marked variations in fluid balance. This is supported by simultaneous measurements of plasma and extracellular volume.

Salt, while it may be effective in maintaining plasma volume and available fluid (NaCSN) at the same levels as observed under pitressin therapy and when fluids are forced, does not abolish the thirst of diabetes insipidus, on the contrary, it increases the polydipsia. (Table I.) This reaction to salt is the same as that seen in the normal person.

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# Radiation Injuries of the Intestines*

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THE purpose of this paper is to discuss radiation injury of the intestine as seen in a series of patients treated for extrarectal pelvic cancer. Gastrointestinal symptoms from radiation were first described by Walsh in 1897; since then numerous reports of lesions so produced have appeared. The increasing use of radiation in the treatment of pelvic cancer, particularly cervical cancer, necessitates a careful study of the incidental injury of the intestinal tract.

In 344 diagnoses of carcinoma of the female reproductive system made by the gynecologic staff of the University Clinics the known incidence of injury of the intestine from irradiation is as follows:

| State of the Carcinoma | No. of Cases | Intestinal Injuries | Percentage |
|---|---|---|---|
| Cervix | 170 | 16 | 9.4 |
| Uterus | 101 | 3 | 2.9 |
| Ovary | 61 | 0 | 0.0 |
| Vagina | 2 | 0 | 0.0 |
| Vulva | 10 | 0 | 0.0 |
| Total | 344 | 19 | 5.5 |

Four of these patients received radiation therapy elsewhere and came to the University Clinics primarily for treatment of complications. In several additional patients the presence of carcinoma immediately adjacent to the site of irradiation made it impossible to evaluate the degree of radiation injury, if any; these have not been included. The nineteen cases are summarized in Table 1.

Mild or acute reactions occur in half to two-thirds of the patients treated by combined x-ray and radium irradiation. An erythema in the rectum or bladder is frequently produced by the dosage required to cure the carcinoma. The reaction may be slight and pass unnoticed, but fairly frequently it is severe. It is evidenced by a burning sensation in the pelvis and by frequency of urination and of defecation. The condition usually clears up within ten days or two weeks, but in severe cases, from four to six weeks may be required. It is in this latter group as Jones[11,12] noted that late rectal and bladder complications may develop, usually six or eight months after the initial irradiation. Acute reactions frequently occur also during the beginning of the third week of external irradiation by x-ray. The mildest symptoms are a slight diarrhea, two to four stools daily, without abdominal pain. In some instances, the symptoms are more severe, six to eight stools daily accompanied by colic-like pain. The diarrhea may be severe and profuse; the stools may be watery or mucoid, sometimes containing blood; nausea and vomiting may occur. These acute phenomena usually clear up completely after the irradiation is stopped. They may subside for a while to be followed sooner or later by a recurrence.

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The diagnosis in the acute reactions is easily established. Sigmoidoscopy discloses a diffuse hyperemia of the rectal mucosa, more marked on the anterior wall. The mucosa bleeds easily when touched. The fatal reactions described by Todd,[14] Mulligan,[13] Cosbie[5] and Cathie[4] (1938) have been observed. Our interest has centered in the chronic ulceration, inflammation and fibrosis occurring as later manifestations and

TABLE I

| Case | Age | Site of Tumor | Irradiation Technic |
|---|---|---|---|
| I | 59 | Corpus | 1. Radium—4,800 mgh. (intra-uterine tandem only)<br>2. X-ray—11,000 r/air (5 portals) |
| II | 55 | Corpus | 1. Radium—5,600 mgh. (intra-uterine tandem only)<br>2. X-ray—10,500 r/air (6 portals) |
| III | 32 | Cervix | 1. Radium—4,900 mgh. (intra-uterine tandem plus 5 needles)<br>2. X-ray—10,500 r/air (6 portals) |
| IV | 47 | Cervix | 1. X-ray—10,500 r/air (6 portals)<br>2. Radium—5,600 mgh. (intra-uterine tandem plus 5 needles) |
| V | 51 | Cervix | 1. X-ray—10,500 r/air (6 portals)<br>2. Radium—4,800 mgh. (intra-uterine tandem plus 5 needles) |
| VI | 70 | Cervix | 1. Radium—4,320 mgh. (2 capsules in crater)<br>2. X-ray—7,100 r/air (6 portals) |
| VII | 31 | Cervix | Irradiation done elsewhere, Radium<br>X-ray |
| VIII | 62 | Cervix | 1. Radium—3,650 mgh. (intra-cervical tandem only)<br>2. X-ray—9,600 r/air (5 portals) |
| IX | 42 | Cervix | 1. Radium—?(4 applications in 15 months. Last application 12 needles)<br>2. X-ray—9,600 r/air (6 portals) |
| X | 59 | Cervix | Irradiation done elsewhere, Radium<br>X-ray |
| XI | 47 | Cervix | Irradiation done elsewhere, Radium<br>X-ray |
| XII | 48 | Corpus | X-ray (after hysterectomy) 5,000 r/air (6 large portals) |
| XIII | 49 | Cervix | 1. Radium—4,800 mgh. (intra-uterine tandem plus 5 needles)<br>2. X-ray—9,600 r/air (6 portals) |
| XIV | 52 | Cervix | Irradiation done elsewhere, Radium<br>X-ray |
| XV | 59 | Corpus | Irradiation done elsewhere, Radium<br>X-ray |
| XVI | 53 | Cervix | Irradiation done elsewhere, Radium |
| XVII | 39 | Cervix | No specific information on dosage in history, Radium<br>X-ray |
| XVIII | 63 | Cervix | 1. X-ray—8,900 r/air (5 portals)<br>2. Radium—3,800 mgh. (intra-cervical tandem plus 3 needles) |
| XIX | 34 | Cervix | Irradiation done elsewhere, X-ray<br>Radium |

* Radium was given first followed by x-ray.
NOTE—All the cases were diagnosed by biopsy or dilatation and curettage.

area involved is variable in size, but usually it extends from about two inches above the anus to the rectopelvic juncture. A small ulcer surrounded by hyperemia may occasionally be found on the anterior wall of the rectum.

Mild early reactions such as these have not been included in our study because they are so common. None of the severe early often difficult to distinguish from neoplastic invasion.[2,3,5,6,8,10,14]

The symptoms of such lesions may appear at any time from shortly after the completion of irradiation to within several months or years later. They consist of abdominal pain, frequent bowel movements, tenesmus and the passage of varying amounts of blood and mucus by rectum. In some cases,

the initial symptoms are those of incomplete intestinal obstruction, i.e., cramp-like abdominal pain, vomiting and obstipation alternating with diarrhea. These may be due to a temporary obstruction caused by hyperemia, edema and spasm of the bowel at the site of the injury or to permanent obstruction caused by a true organic stricture.

On rectal examination proctitis and ulceration is felt as a slight irregularity at the level of the cervix with thickening of the mucosa. In perirectal fibrosis there is marked fixation of the entire rectum thus increasing the confusion with an extensive carcinoma. In some instances, a very narrow stricture may prevent the passage of the finger. Occasionally, it is impossible to

TABLE I (*Continued*)

| Approximate Tissue Doses in Rectosigmoid Region | | Gastrointestinal Symptoms |
|---|---|---|
| 10,000–30,000 r in 2 days<br>3,000– 4,600 r in 37 days | 41 days | Diarrhea, obstipation |
| 12,000–24,000 r in 2 days<br>2,100– 3,100 r in 31 days | 38 days | Diarrhea, constipation, bloody stools |
| 10,000–25,000 r in 2 days<br>3,200– 4,700 r in 39 days | 44 days | Abdominal cramps, rectal bleeding, diarrhea |
| 3,600– 6,000 r in 31 days<br>12,000–30,000 r in 2 days | 33 days | Progressive constipation |
| 2,400– 3,800 r in 34 days<br>10,000–25,000 r in 2 days | 112 days | Diarrhea |
| 15,000–22,000 r in 2 days<br>2,000– 3,000 r in 37 days | 40 days | Vomiting, diarrhea, intestinal obstruction |
| Not estimated | | Constipation, nausea, vomiting |
| 8,000–24,000 r in 3 days<br>2,800– 4,200 r in 43 days | 48 days | Bloody diarrhea |
| ? 15 months<br>2,800– 3,600 r in 29 days | 2 years | Abdominal distress |
| | | Diarrhea, abdominal pain, bloody stools<br>Nausea, bloody diarrhea |
| 2,200– 6,000 r in 24 days | | Bloody stools, diarrhea, alternately constipation |
| 10,000–25,000 r in 2 days<br>2,400– 3,350 r in 65 days | 68 days | Diarrhea |
| | | Diarrhea, intestinal obstruction<br>Vomiting, abdominal pain<br>(Terminal case)<br>Rectal bleeding, abdominal pain<br>Diarrhea, bloody stools |
| 3,000– 4,700 r in 35 days<br>12,000–22,000 r in 2 days | 52 days | Diarrhea, bloody stools |

| Case | Type of Injury | Outcome |
|---|---|---|
| I | Ulceration stenosis | Died; colostomy, infiltration of tumor |
| II | Stenosis | Resection of sigmoid stricture |
| III | Proctitis | Incomplete obstruction sigmoid (10 months) |
| IV | Stenosis | Resection of sigmoid stricture |
| V | Stenosis | Extension of tumor? |
| VI | Stenosis | Resection of ileal strictures |
| VII | Ulceration | Died; extension of tumor; x-ray fistula |
| VIII | Ulceration | Ulceration spontaneously improved |
| IX | Stenosis, telangiectases | Carcinoma progressed |
| X | Stenosis | Carcinoma progressed |
| XI | Stenosis | Incomplete obstruction sigmoid |
| XII | Stenosis | Incomplete obstruction sigmoid |
| XIII | Stenosis | Incomplete obstruction sigmoid; metastases |
| XIV | Stenosis | Suicide; stenosis sigmoid |
| XV | Ulceration | Died; peritonitis, perforation ulcer |
| XVI | Ulceration | Died; widespread metastases |
| XVII | Massive necrosis colon | Colostomy; peritonitis; died; necrosis colon |
| XVIII | Proctitis | Spontaneous improvement |
| XIX | Ulceration | Died; infiltration of tumor |

reach the lesion with the finger and even proctosigmoidoscopy may not be decisive. The examination is usually very painful.

On sigmoidoscopy the typical ulcer, usually situated on the anterior rectal wall, is greyish white in color with an exudate of blood and pus in the base and surrounded by telangiectases. In perirectal fibrosis occlusion of the rectal lumen occurs more frequently; there may be no ulceration.

Roentgen studies are advisable when proctoscopy does not reach the lesion or when endoscopy is impossible. Barium enema or barium and air double contrast studies are much more satisfactory than the barium meal. The characteristic roentgenologic picture is illustrated in Figures 2 to 5.

Biopsy is somewhat hazardous because of the danger of perforation and fistula formation. If biopsy is desired, more than one piece of tissue should be taken from different places around the edge of the ulcer.

The decisive diagnosis between malignancy and irradiative injury may finally be made only by the improvement in general health following adequate treatment, relief of the intestinal symptoms and roentgen evidence of increasing size of the lumen of the bowel. In others the diagnosis may be confirmed only after resection of the process sometimes months after colostomy has been performed for the relief of acute symptoms.

Pathologically in the acute mild reactions, there is inflammation with edema of the mucosa with or without fibrinous deposits over the surface and with or without ulceration.[7] The chronic lesions consist principally of inflammation with ulceration and sclerosis or combinations of the two; fistulas and strictures are frequent.[15] The ulcerations range from irregular superficial areas of desquamation to deep, punched out ulcers. Telangiectases occur at the edges of the ulcerations. Stenosis is due to diffuse sclerosis with general constriction or to a stricture at the site of ulceration. Histologically, edema is seen early together with progressive hyaline thickening in all layers of the wall and also in the vessels. Thrombosis and vascular sclerosis are prominent. The mucosa is focally destroyed. Degeneration and atrophy of the muscular coats may be present together with edema and vacuolization. The combination of atrophic fibers, swollen fibers and hyaline interstitial fibrosis is very striking. Figures 6 to 8 illustrate various phases of the reaction.

It is difficult in these injuries to evaluate the respective rôles of roentgen and radium irradiation; the former are probably responsible for the widespread lesions and the latter for those localized to the immediate neighborhood of cervix, uterus and vagina. In most cases, a summation effect is present. The radiotherapist is today equipped with rather detailed information on the quantitative distribution of radiation under variable conditions. This enables him to correlate treatment and reaction more exactly than was possible a decade ago. Both types of irradiation are better tolerated by the normal tissues if given at low intensities over longer periods than as massive doses in short times. In spite of the fractionation of x-rays, single doses can be high enough to cause vascular damage. A moderate figure of roentgen units can mean an overdosage if it is given together with a large amount of radium in a short time. The distribution of radium also plays an important rôle, for if it is placed improperly damage may occur even though the dosage and time intervals are correct. These problems of radiologic technic are mentioned to illustrate the importance of a well trained radiologist for the scrupulous planning of the combined treatment and also for the help he may be able to give in the differentiation of radiation sequelae and progressive cancer by means of information obtained from the details of dosage and technic.

It is possible that certain conditions may predispose to radiation injury of the intestine. Jones[12] suggested that pelvic inflammatory disease might fix the bowel in the pelvis and thus increase the exposure. Such a theory may explain the lesion found in the ileum in Case VI. This patient had pyometra associated with carcinoma of the cervix.

Aldridge[1] suggested that the accidental dislodgement of radium applicators from the cervical canal or uterine cavity to the vagina, retroversion of the uterus and the presence of peritoneal adhesions, fixing one or more loops of the intestine to the external surface of the uterus or to the cervical stump, might result in an excessive exposure. There is some evidence that diabetes and hyperthyroidism render the bowel more susceptible. It seems apparent, however, that frank overdosage is the most important factor. The individual variations in radio sensitivity are probably of minor importance. A dose well tolerated by the average patient should not cause severe irreversible and irreparable damage in any patient.

## TREATMENT

In the treatment of the acute reactions, symptomatic medical treatment is usually satisfactory. Rest in bed, a bland diet, rectal instillations of warm oil, antispasmodics and sedatives are helpful. The more severe cases should be treated very carefully; dehydration and metabolic changes must be combated by means of parenteral fluids, saline, glucose and protein as indicated. Direct treatment of the rectal lesion by means of rectal irrigations with saline or weak antiseptics is probably of little value. The local application of radon-impregnated vaseline introduced by Whemann in 1928 might be beneficial if a satisfactory mode of application could be devised.

Surgery may be required because of stenosis, bleeding or pain. A colostomy is imperative when the stenosis is marked. With incomplete obstruction due primarily to edema, conservative management may afford relief. Recurrent bleeding is occasionally severe enough to require colostomy. Persistent severe pain is at times a most difficult manifestation and may be relieved by presacral sympathectomy. In some cases both colostomy and presacral sympathectomy may be required. Resection of the inflamed portion of bowel is seldom necessary for healing usually occurs eventually. With resolution of the lesion, the stenosis lessens. Fistulas should be closed surgically unless they heal spontaneously in a reasonable time.

Wigby (1943) reports six colostomies in his series and Todd (1938) seven, all with excellent results. Bacon (1937) performed eight colostomies in fourteen patients with strictures.

In treatment, a great deal of attention must be given to the psychosomatic factors. Cancer-phobia is almost always present and necessitates a careful explanation of the nature of the condition. The diet will be varied according to the predominance of either constipation or diarrhea. Phenobarbital and belladonna are of some value.

Our experience may be best presented perhaps by a summary of the material and by descriptions of each case:

## CASE REPORTS

CASE I. M. V., age fifty-nine, (245770) a diabetic with carcinoma of the corpus uteri, in July, 1944, received 4800 mgh. of radium (50 mg. for 96 hr.; 1 capsule 2 cm. in length). The x-ray treatment consisted of 10 × 300 r. including backscatter to each of four pelvic portals plus 5 × 300 r including backscatter to one perineal portal, from July 31, 1944 to August 28, 1944. Severe diarrhea appeared two months after the treatment followed a month later by constipation and partial intestinal obstruction. A colostomy was performed January 5, 1945. Proctoscopy some days later revealed a

sloughing ulcer in the rectum with marked edema of the rectal walls. A complete hysterectomy with bilateral salpingo-oophrectomy in July, 1945, disclosed malignant tissue in the uterus. Death occurred in February, 1946, after a febrile terminal course. At autopsy a fibrous stricture of the rectum 1.5 cm. in diameter, located 8 cm. above the anus was found. Metastatic carcinoma was present in the vagina.

*Comment.* This is an instance of frank radiation ulcer and stenosis of rectum. It also illustrates the problem of the proper distribution of radium because 4800 mgh. are usually tolerated if the radium is spread out over an area of 8 to 12 cm.$^2$ in the uterus rather than contained in a capsule only 2 cm.$^2$ The diabetes may have decreased the resistance to irradiation and to superimposed infection.

CASE II. F. B., fifty-five years of age, (264391) with carcinoma of the corpus uteri, received 5,600 mgh. of radium (100 mg. in fifty-six hours) in two capsules with a total length of 4 cm. on July 23, 1941. From August to September 2, 1941, she received x-ray treatments (10 × 300 r to four anterior and posterior pelvic portals and 4 × 300 r to two lateral pelvic portals), a total depth dose of 2,100 r to each parametrium and a possible maximum dose to the rectosigmoid of 3,400 r being delivered. About six months after the end of the treatment diarrhea developed alternating with constipation and accompanied by bloody stools. Symptoms of intestinal obstruction were present one month later. X-ray in March, 1942, showed marked obstruction of the lower sigmoid. At abdominal operation in March, 1942, no cancer was seen but there were adhesions of the sigmoid to the corpus uteri and a large patch of necrotic tissue was found in the sigmoid. A complete hysterectomy with bilateral salpingo-oophorectomy was performed. No cancer was found histologically. Resection of the sigmoid was performed six months later; no cancer was present, only "an area of constriction with fibrosis of the muscularis 3 cm. wide." In 1943, the patient was reported in good condition.

*Comment.* In this instance of stenosis of the sigmoid in an obese woman the post-radiation changes were well localized and again apparently resulted from the intensive local radium effect.

CASE III. M. V., thirty-two years of age, (154145) was discovered in the fifth week after delivery, to have cancer of the cervix. A capsule of 50 mg. of radium and 5 capsules of 10 mg. each were placed in the posterior lips of the cervix only, for forty-nine hours on January 14, 1943. On January 19, 1943, x-ray treatment was started: 10 × 220r/eff. to two anterior and two posterior pelvic portals and 4 × 220r/eff. to two lateral portals, instead of the perineum, because of the postpartum state and the local radium. The patient had diarrhea during the treatment, stopping at the end and recurring after one week for a few days. About four months after the end of treatment the patient complained of abdominal cramps, rectal bleeding and severe diarrhea. Proctoscopy at that time, August, 1943, showed an edematous, easily bleeding mucosa. X-ray in November, 1944, revealed "narrowing at the rectosigmoid junction not producing obstruction." (Fig. 1.)

Pelvic examination in November, 1944, at the time of the patient's last visit disclosed no evidence of recurrent carcinoma. The vault was clean; the cervix was not seen; the corpus could not be felt. A rectal structure was felt at the tip of the examining fingers; the walls of the rectum were firm, fixed and indurated.

*Comment.* The proctitis was attributed to local injury of the anterior rectosigmoid wall from the radiation in the immediately adjacent posterior lip of the cervix. The radium dosage was very considerable and it was localized; the roentgen irradiation in itself was not excessive but it was superimposed on the radium.

CASE IV. (Fig. 2.) G. H., thirty-seven years of age, (264832), with cancer of the cervix in stages III and IV extending into the vaginal wall, diagnosed in June, 1941, received roentgen irradiation 10 × 220r/eff. to two anterior plus two posterior pelvic portals plus 4 × 220r/eff.

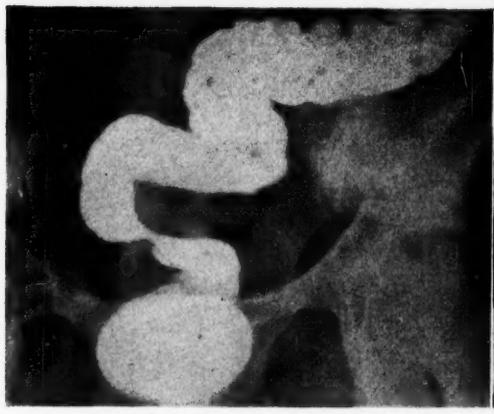

FIG. 1. Case III. Smooth stenotic deformity of the rectosigmoid twenty-two months after irradiation of the cervix uteri.

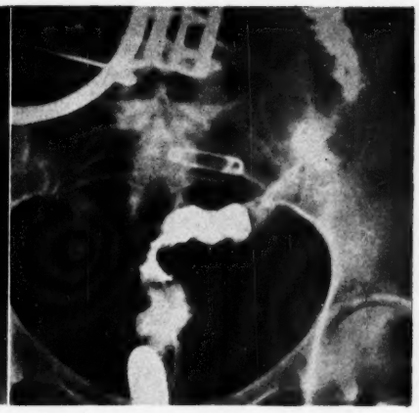

FIG. 2. Case IV. Stricture of the rectosigmoid subsequently resected and shown to be benign.

to two lateral pelvic portals, in thirty-one days, from June 26th to July 26th, 1941; radium was used in September 9 to 11, 1941, 1 capsule of 50 mg. and 5 of 10 mg. for fifty-six hours, a total of 5,600 mgh. Severe and progressive constipation appeared two months later necessitating colostomy in January, 1942. In May, 1943, a stricture at the rectosigmoid junction was resected. No histologic evidence of carcinoma was found in the resected bowel.

*Comment.* This is an instance of post-irradiation intestinal stricture in advanced cervical carcinoma involving the vagina. Interstitial radium seemed indicated in higher than routine dosage because of the extent of the tumor and even though the rather thin patient had already received a relatively high dosage of roentgen irradiation.

CASE V. I. W., fifty-one years of age, (271594), with carcinoma of the cervix, stages III and IV received 10 × 220r/air to each of two anterior plus two posterior pelvic portals and 4 × 220r/air to two lateral pelvic portals in thirty-four days from October 3, 1941, to November 5, 1941. Radium was given on January 20, 1942, 100 mg. for forty-eight hours, a total of 4,800 mgh. Diarrhea was present in April, 1942, but improved in June. In November, the patient complained of backache and vaginal discharge. X-ray in January, 1943, showed "narrowing at the rectosigmoid junction." In February, 1943, there was induration and fixation of the wall of the rectum. In December, 1943, there was no evidence of vaginal recurrence but rectal examination revealed the entire pelvis to be filled with a firm mass. The rectum admitted only one finger. The patient has not been seen since that time.

*Comment.* The case is included in the present series because of the rather typical symptoms and roentgenologic manifestations. The pelvic tumor, however, seems surely attributable to uncontrolled, progressive carcinoma. The absence of cervical recurrence is rather common in the pelvic progression of cancer.

CASE VI. L. H., seventy years of age, (156236), with carcinoma of the cervix and pyometra (incision and drainage) together with stenosis of the vagina received radium treatment on August 11 to 13, 1936, 2 capsules for forty hours, 4,320 mgh. X-ray therapy was given from August 14 to September 19, 1936, 4 × 300r/air to each of six portals.

Epigastric pain and vomiting were present in November, 1936. From 1937 to December, 1940, she developed recurring attacks of diarrhea with frequent attacks of upper abdominal pain and accompanied by hyperchromic anemia. Intestinal obstruction developed in December, 1940. X-ray examination disclosed obstruction of the ileum. At operation 50 cm. of ileum were resected because of an annular constriction at two points of the ileum together with an enterolith 4 by 2½ cm. There was no evidence of cancer. (Fig. 3.)

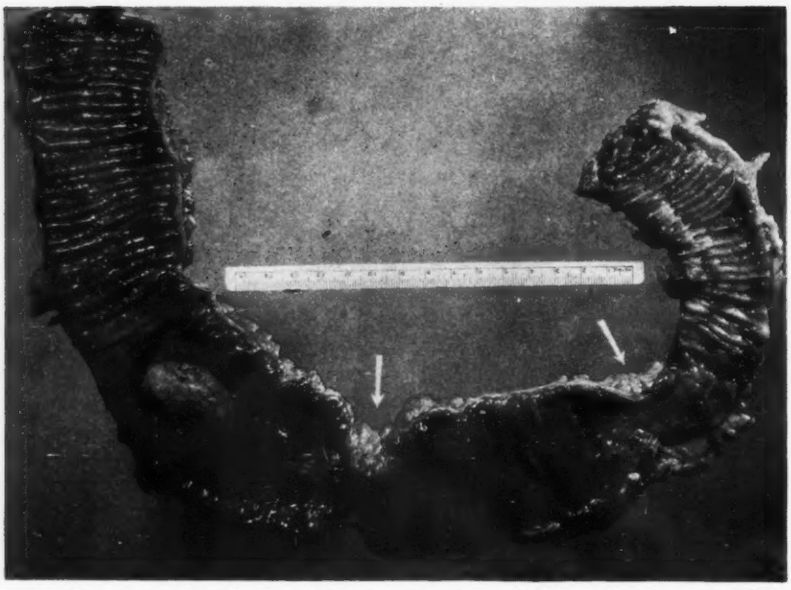

FIG. 3. Case VI. Postirradiation strictures of the ileum with a ball-valve enterolith.

*Comment.* This is an instance of postirradiation stenosis of the ileum. Fixation of the ileum in the pelvis after inflammatory disease (pyometra) may have predisposed the bowel to injury. The dose of radium was not excessive, but it was given with high intensity; the placement was possibly not well controlled because of a narrow vagina. The x-ray therapy was administered more rapidly than is customary at present.

CASE VII. B. O., thirty-one years of age, (19007) a diabetic with septate vagina, was found to have carcinoma of two cervical stumps in 1930. In 1920, she had undergone a hysterectomy with left salpingo-oophorectomy for fibroid degeneration of the uterus. Five years earlier the right tube and ovary had been removed. Before the first operation the patient had pelvic gonorrhea. On February 14, 1930, she received radium implantation: 1 capsule of 50 mg. for twenty-five hours-2,500 mgh. in each orifice. The following x-ray treatments were given:

1. 550 r/air to ant. and post. pelvis on Feb. 19–24, 1930
2. 628 r/air to ant. and post. pelvis on May 19–20, 1930
3. 628 r/air to ant. and post. pelvis on July 19–25, 1930
4. 628 r/air to ant. and post. pelvis on Oct. 8–22, 1930
5. 472 r/air to ant. and post. pelvis on Dec. 15–22, 1930

2906 r/air — in 10 months (two portals only)

After the first x-ray treatment she was seen in the gastrointestinal clinic with general abdominal complaints: constipation, nausea and vomiting. On April 28, 1930, at proctoscopy, "there was some diffuse pallor of the mucous membrane, but no evidence of cancer." X-ray of the colon in May, 1930, was normal. The patient died on April 3, 1931. Autopsy revealed cancer in the vagina, posterior wall of the bladder and the anterior wall of the rectum. About 2.5 cm. above the anal orifice an opening of the rectum was observed into a larger cavity occupying most of the pelvic region. There was fibrous induration of the pelvic connective tissue with obstruction of the sigmoid colon. Histologically, the colonic mucosa appeared somewhat atrophic; the submucosa was fibrotic and infiltrated with round cells.

*Comment.* This is an instance of progressive cancer in scarred pelvic tissues. The radium irradiations were given only to a small area which may therefore have re-

covered relatively well in spite of the high dosage. The case is included as an instance of irradiation injury because of the typical location of the lesion in the rectum and the fibrosis noted in the submucosa of the rectosigmoid. As so often happens, it is difficult completely to separate the rôles played by the radiation and the neoplastic invasion.

Case viii. C. T., sixty-two years of age, (92722), with cancer of the cervix, underwent a vaginal operation for cystocele in April, 1943. Previously she had had an appendectomy, salpingectomy and excision of a fistula in ano. Radium was inserted on April 29, 1943, 1 capsule of 50 mg. for seventy-two hours—3600 mgh. in a surface of 2 cm. Beginning May 4, 1943, x-ray irradiation was instituted 10 × 300 r/eff. to two anterior and two posterior pelvic portals and 4 × 300 r/eff. to two lateral pelvic portals in forty-two days. (See data in summary for total dosage.) On February 8, 1944, the patient complained of bloody diarrhea with cramps. X-ray examination disclosed no obstruction but there was a suspicion of an ulcer fleck on the anterior rectal wall. The patient gradually improved and in May, 1945, was feeling much better with diarrhea occurring only occasionally.

*Comment.* This is interpreted as an ulcer of the anterior rectal wall due to the localized high dosage of radium and the superimposed roentgen irradiation.

Case ix. A. F., forty-two years of age (150540), received an unknown amount of radium therapy elsewhere for cancer of the cervix on two occasions. About six months after the last treatment (September, 1935) abdominal distress appeared with some blood in the stools and low back pain. In May, 1936, a nodular tender mass in the left parametrium was found. It was thought to be adherent but not definitely fixed to the cervical stump. A diagnosis of recurrent carcinoma with extension to the left parametrium was made. X-ray treatment was started in May, 1936, 9 × 200 × 6 pelvic portals. (See data in summary for total dosage.) At proctoscopy there was narrowing with painful spasm at 15 cm. with no ulceration, but a few tiny blood clots were adherent to the rectal wall.

*Comment.* Progressive cancer was evidently present in the left parametrium. The proctoscopic findings are suggestive of radiation injury, but complete differentiation in this instance is not possible.

Case x. L. R., fifty-nine years of age (240852), had had a diagnosis of carcinoma of the cervix grade ii made at another hospital for which she received a total dose of 6,000 mg. hours of radium in April, 1940. From May 3 to June 11, 1940, she received 10 × 220 r/air to each of four pelvic portals and 4 × 220 r/air to a perineal portal for a total tissue dose of 3,120 r in the parametrium. In November, 1940, she began to have diarrhea associated with cramp-like lower abdominal pain and blood in the stools. X-ray and proctoscopic examinations revealed a narrowing of the colon for a distance of 8 cm. beginning 15 to 18 cm. above the anus. She complained of blood in the stools intermittently the next three years. In April, 1944, she was hospitalized because of weakness, pain in the left upper extremity and shoulder and tenderness over the left costal margin. X-ray of the chest revealed bilateral pulmonary metastases. The patient died in September, 1944, in another hospital.

*Comment.* The patient evidently died from metastatic carcinoma of the cervix. The diagnosis of post-irradiation sigmoiditis is based upon the bloody diarrhea appearing seven months after a large dose of radium and also upon the roentgenologic appearance of the sigmoid. (Fig. 4.)

Case xi. M. G., forty-seven years of age (253635), was treated for cancer of the cervix by radium and x-ray at another hospital in April, 1940. The patient experienced nausea and diarrhea with mucus and blood during the irradiation. In November, 1940, a small amount of red blood appeared in the stools. Proctoscopy on December 6, 1940, revealed "an area of fibrosis at 10 and 14 cm. Free blood was present, coming from beyond the fibrosis." X-ray examination on December 7, 1940, disclosed a

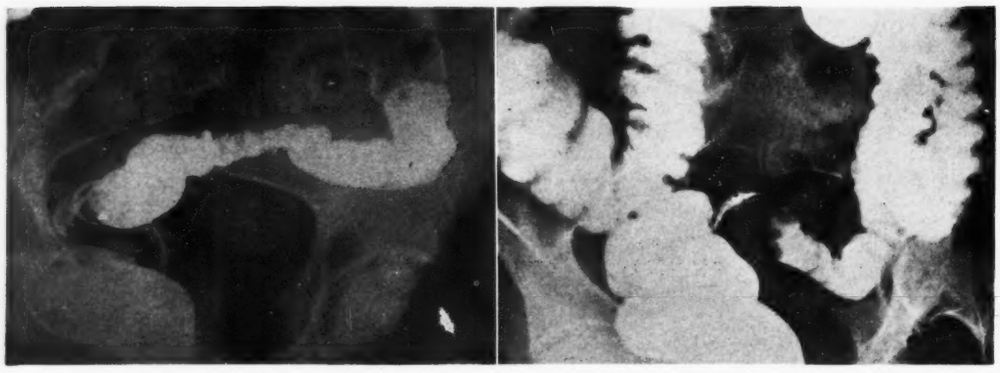

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FIG. 4. Case x. Moderate deformity of the sigmoid eight months after irradiation.
FIG. 5. Case XII. Stricture of the rectosigmoid six months after hysterectomy and roentgen irradiation of the pelvis for carcinoma of the corpus uteri.

peculiar narrowing of the rectosigmoid confirmed at another examination December 11, 1940. On February 18, 1941, the patient wrote that the bleeding from the rectum was very little but she did not return to the clinic.

*Comment.* The diagnosis in this case also is based on the appearance of bloody diarrhea after irradiation of a cancer of the cervix together with the proctoscopic and roentgenologic findings. A biopsy of the rectal stricture was negative for carcinoma.

CASE XII. (Fig. 5.) J. M., forty-eight years of age (273559), had an incomplete hysterectomy and bilateral salpingo-oophorectomy in June, 1941, at another hospital for cancer of the corpus uteri. X-ray therapy was given after the operation (5900 r depth in six portals). In December, 1941, she passed some blood per rectum. A mass was felt in the left cul-de-sac. Proctoscopy on January 3, 1942, was considered normal. At another proctoscopy on January 9, 1942, the mucosa was described as mildly edematous. Difficulty was encountered in passing the instrument beyond 10 cm. On May 21, 1942, at the third proctoscopy the mucosa was described as bleeding more easily than normal and the same difficulty in passing the instrument beyond 10 cm. On May 21, 1942, at the third proctoscopy the mucosa was described as bleeding more easily than normal and the same difficulty in passing the instrument was encountered. A proctoscopic biopsy disclosed no evidence of carcinoma.

Diarrhea was still present alternating with constipation. X-ray examination of the colon in January and again in June, 1942, disclosed a narrowing of about 8 cm. of the rectosigmoid interpreted as probable post-irradiation change. (Fig. 5.) The patient was not seen again.

*Comment.* This patient received no radium and the dosage of roentgen irradiation was not unusual. However, the roentgenologic and proctoscopic findings were considered more characteristic of radiation injury than of neoplastic invasion. Conclusive evidence, however, is not available.

CASE XIII. M. S., forty-nine years of age (199025), with cancer of the cervix graded III and IV had had an appendectomy and oophorectomy in 1914. Radium was inserted on June 7, 1938 (100 mg. for forty-seven hours-4700 mgh., interstitial method). X-ray therapy was given 9 × 300 r/eff. to two anterior and two posterior pelvic portals and 7 × 300 r/eff. to two lateral portals, from June 10 to September 30, 1938. (See data in summary for total dosage.) Diarrhea appeared during treatment and lasted only a few weeks. In April, 1943, x-rays examination disclosed "narrowing of the rectosigmoid junction, probably due to fibrosis." The patient has not been seen since October, 1943, when she received x-ray therapy for metastases.

*Comment.* The diagnosis in this case is based upon the appearance of diarrhea during the roentgen irradiation and subsequent to the radium and also upon the

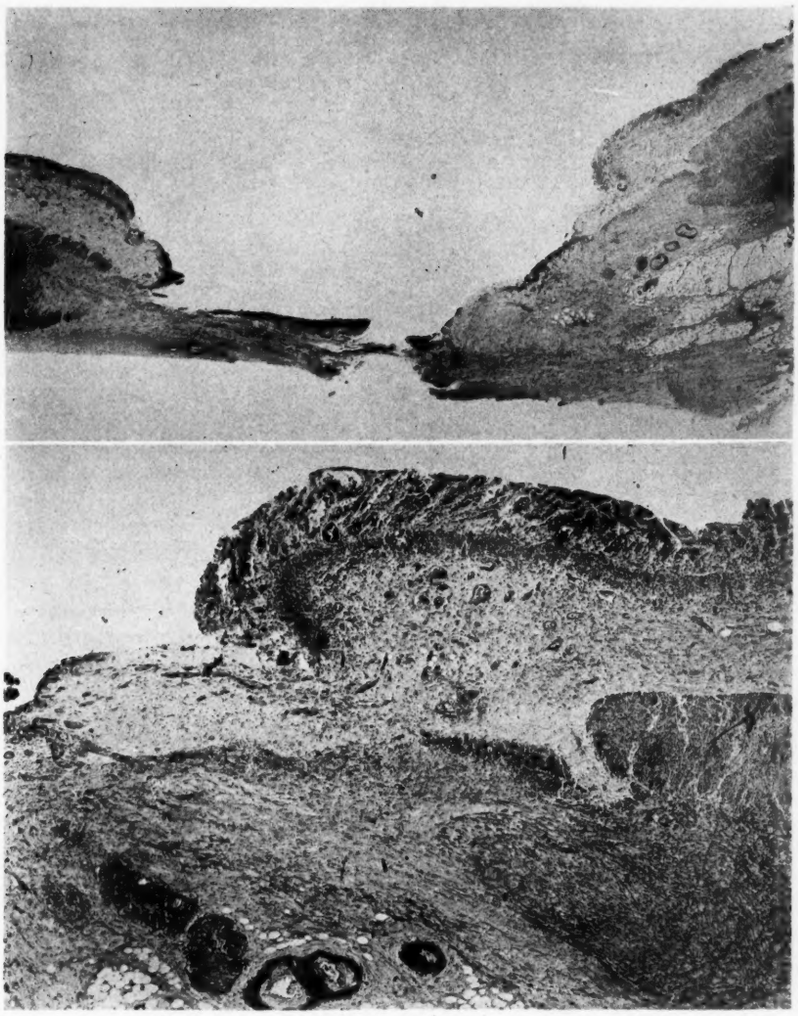

FIG. 6. Case XV. Deep chronic ulcer of the colon, with a perforation in its floor where scar tissue has replaced the muscle coats (hematoxylin and eosin, × 8). FIG. 7. Case XV. Margin of ulcer illustrated in Figure 6, showing edema, fibroplasia and telangiectases in the submucosa; fibrous tissue replacing the muscle coats; thick-walled hyalinized arteries and thrombosed veins (hematoxylin and eosin, × 30).

roentgenologic demonstration of narrowing of the rectosigmoid four and a half years later.

CASE XIV. C. A., fifty-two years of age (184320), with cancer of the cervix received radium treatment on September 30, 1937 (100 mg. for thirty-six hours-3600 mgh.). A febrile period followed. Roentgen irradiation was given 5 × 200 r/air to six pelvic portals from October 4, 1937, to October 23, 1937, and 3 × 200–300 r/air to three pelvic portals from November 5, 1937, to November 26, 1937. Another radium treatment was given in January, 1938, (100 mg. × 24 hours-2400 mgh). After two weeks of diarrhea, tenesmus and abdominal soreness the patient developed acute intestinal obstruction requiring a colostomy on March 16, 1938. X-ray examination March 14, 1936, had shown a "high grade obstruction to the passage of barium in the mid-sigmoid for 5–6 cm." A pelvic abscess was drained in April. In October the colostomy was closed.

On November 1, 1938, the patient leaped from a window of the hospital. Autopsy revealed apparent cure of the cancer, "status post-irradiation" with stenosis of the sigmoid and obstruction of the left ureter. Microscopic studies

showed hyalinized fibrous tissue with sclerotic vessels containing foci of round cells but no tumor.

*Comment.* The stenosis of the sigmoid seems definitely attributable to the radium and roentgen irradiation.

Case xv. (Figs. 6 and 7.) M. F., fifty-nine years of age (221852), with adenocarcinoma of the uterus and diabetes mellitus received radium treatment June 17, 1939 (5000 mgh.) and the routine x-ray treatment (10 × 220 to two anterior and two posterior pelvic portals and 3 × 220 to two lateral pelvic portals) in about eighty days. Recurrence of the tumor was found and a second radium treatment was given on October 25, 1940 (100 mg. × 36 hours-3600 mgh.). Another course of x-ray therapy was given in twenty days; (3 × 230 × 7 portals, October 1940). Cauterization of intracervical cancer with acetone was performed September 9, 1941 (recurrence).

On October 14, 1941, the patient developed vomiting, fever and severe abdominal pain. Death occurred on October 31, 1941. Autopsy revealed fibrinopurulent peritonitis, cancer of the uterus filled with necrotic masses; the rectum contained a sharply circumscribed deep ulcer 18 by 14 mm. in size and about 3 to 4 mm. deep. The floor of the ulcer was dark greenish-grey. Through a perforation in the floor of the ulcer a 2 mm. probe passed readily into the pouch of Douglas.

*Comment.* Progressive cancer, irradiation ulcer in the rectum and peritonitis presumably from perforation of the ulcer were present. With the large amount of necrotic tissue in the uterus the peritonitis may have been present before the perforation. The diabetes may have decreased the resistance to irradiation. The dose (x-ray and radium) surpassed the tolerance dose purposely in the palliative attempt to decrease the hemorrhage.

Case xvi. M. B., fifty-three years of age (223852), was admitted for cancer of the cervix with lung and liver metastases too advanced for further therapy. Four radium treatments, amount unknown, had been given elsewhere.

The patient died on August 8, 1939. Autopsy revealed cancer of the cervix with metastasis into the broad ligaments, pelvic lymphatic glands, lungs and liver. An ulcer was found on the rectal wall, behind the cervix, 3 cm. in diameter, round, penetrating the entire thickness of the rectal wall at its deepest point (radium ulcer).

*Comment.* This patient was apparently treated very inadequately, with radium only, causing local damage without reaching the distant points of the carcinoma. The symptoms due to radiation injury were not discernible clinically.

Case xvii. (Fig. 8.) P. G., thirty-nine years of age (351346), received three radium and thirty-six x-ray treatments (dosages not available) for carcinoma of the cervix at another institution in 1940. Rectal pain started after x-ray therapy. Approximately four years after the last treatment, the patient noted bleeding from the rectum and the appearance of abdominal pain. Colostomy for the relief of the abdominal pain was performed in February, 1944. Exploration of the intestine and closure of the colostomy was carried out on February 12, 1945. Peritonitis developed ten days later; death occurred March 4, 1945. Necropsy revealed diffuse peritonitis and a massive necrosis of the colon a short distance above the site of repair of the colostomy. Sections taken from the region of the colostomy showed an increase in fibrosis with an occasional suture thread or pus pocket present. One small area consisted almost entirely of multinuclear giant cells. Sections from the stricture of the sigmoid 14 cm. above the anus showed edema with submucosal and adventitial fibrosis but with no evidence of carcinoma.

*Comment.* Overdosage not only locally but over a large area was apparently responsible for the extensive injury.

Case xviii. M. P., sixty-three years of age (306990), with a squamous cell carcinoma of the cervix received a total of 5,000 roentgen units

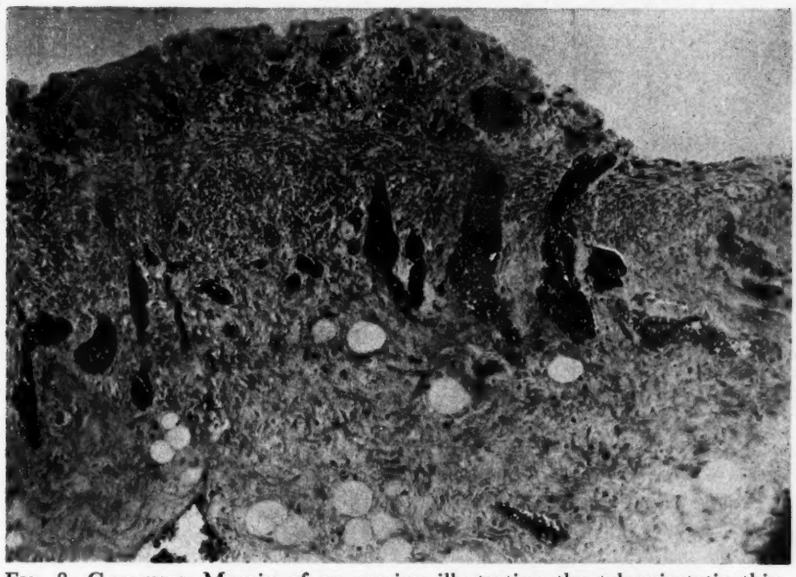

FIG. 8. Case XVII. Margin of an erosion illustrating the telangiectatic thin-walled blood vessels, the atrophic mucosa and the submucosal fibroplasia of chronic irradiation injury. (The superficial epithelium has sloughed post-mortem.) (Hematoxylin and eosin, × 110.)

to the upper end of the vagina and pericervical region and 2800 r. units to the parametria at the wall of the pelvis between April 22, and September 11, 1943. In May the x-ray therapy had to be interrupted because of diarrhea. Radium treatment was given between June 10th and 12th for a total of 3,800 mgh.

The patient was seen October 16, 1944 at which time she complained that daily for a year she had had from one to three loose stools containing small amounts of bright red blood. Proctoscopy to 10 cm. showed a normal mucosa but some bloody mucus was present in the lumen. The rectosigmoid region was very active; the proctoscope could not be advanced further because of pain. Mild inflammatory changes were noted in the rectosigmoid on fluoroscopy. There has been no recurrence of symptoms.

*Impression.* Mild radiation injury lasting longer than usual but without demonstrable ulceration or marked stenosis.

CASE XIX. (Fig. 9.) R. S., thirty-four years of age (298154), with carcinoma of the cervix was given x-ray therapy but it had to be discontinued because of continued bleeding in spite of repeated transfusions of whole blood. Later the x-ray therapy was resumed in the Out-Patient Department, the patient receiving between December 9, 1942, and January 23, 1943, a total of 4,300 r. to the cervix. She was given 3,400 mgh. of radium to the corpus, cervix and cervical canal. By November 12, 1943, she complained of a mass in the vagina with severe pelvic pain, diarrhea and bloody stools. By February 15, 1944, nausea, vomiting and abdominal distention were added to the previous complaints. The patient's final admission was on April 7, 1944. Opiates and cobra venom were given because of severe pain. Death occurred on April 12, 1944.

Autopsy revealed extensive ulceration and sloughing of most of the cervix; carcinomatous infiltration of the parametrium, vaginal wall, and urinary bladder; large vesico-vaginal fistula with complete destruction of the ureteral orifices and distal ends of the ureter; post-irradiation ulcers and atrophic-fibrotic changes in the colon just above the rectosigmoid junction; kinking of the colon and adhesive fixation to the uterine corpus in the ulcerated region.

Histologically, a section from the region of irradiation injury shows a flat sclerotic ulcer infiltrated by polymorphonuclear cells. There is increased connective tissue in the submucosa, in the serosa and in a dense fibrous adhesion.

FIG. 9. Case XIX. Typical radiation ulcer showing marked telangiectases; autopsy specimen.

*Comment.* This patient with extensive inoperable cancer of the cervix received moderate amounts of radium and roentgen irradiation; at autopsy fifteen months later definite evidence of radiation injury of the bowel was present.

## SUMMARY

The outstanding early symptom of radiation injury of the intestine is diarrhea, mild to severe in degree. Later manifestations are pain, demonstrable ulceration and stricture formation with partial or complete obstruction. The early lesions, located usually on the anterior wall of the rectum and rectosigmoid, are characterized by an edematous friable mucous membrane. Later ulceration, with a grayish white slough, occurs at the level of the cervix. In time perirectal fibrosis resembling a "frozen" pelvis may develop and result in obstruction. In the severe injuries with stenosis, hemorrhage or persistent severe pain, temporary or permanent colostomy may be required with or without resection of the bowel. Intractable pain may be treated by colostomy and resection of the afferent nerve supply to the rectum. The ideal therapy is, of course, prophylactic, the avoidance of radiation injury. Whether or not it is possible by attention to the details of technic to administer effective carcinocidal doses of irradiation without occasional severe injury to adjacent normal tissue such as the rectum seems questionable at present.

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# Lichen Planus, Atypical

## *A Report of Ten Cases*

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LICHEN planus manifested itself among troops in the Southwest Pacific Area in a manner hitherto never observed. Army medical authority directed that the disease be labeled "lichen planus, atypical." When sufficient data have been accumulated and studied a more specific term will undoubtedly be assigned. On searching through four recent editions of standard textbooks only one description was found which seemed applicable to the cases herewith presented. The elder Sutton[1] wrote that he had seen two rare cases of lichen planus in which large, purplish papules with stellate bases had coalesced at various points to form a net-like arrangement. His diagnosis was "lichen planus hypertrophicus, retiformis." All but one of the patients in this series showed this same process which is called "reticulation" in Table I. The exception, Case X, had far less active lesions than the others, the nodules lacking the finger-like offshoots upon which strand formation apparently depends.

### CASE REPORTS

CASE I. A forty-two year old lineman entered the hospital on February 17, 1944, with a generalized eruption of a month's duration.

He had gone to New Guinea in July, 1943. In October he noticed small blisters on the inner sides of both wrists which itched intensely, especially at night. Since his work brought him into contact with all types of vegetation, a diagnosis of dermatitis venenata was made and calamine lotion was prescribed. The blisters soon dried up but the skin remained rough, red and irritated. Two months later groups of blisters broke out on the inner aspects of both thighs. This eruption cleared entirely with the same lotion.

In January, 1944, the skin of the upper anterior chest grew rough with a myriad of tiny, pointed elevations each having a whitish core which could be expressed as a needle-like plug. This matter could easily be pulverized between the fingers and rubbing the roughened skin produced a powdery shower. A similar process soon developed over the neck, arms and legs and within a few days became generalized. Itching was the only distressing symptom.

Within a matter of days the "roughness wore off, leaving purplish spots which were raised." The latter tended to run together and grew scaly; thereupon, the itching ceased. About three weeks later he arrived at this hospital.

The family history was negative for skin disease and not remarkable for allergy. Several times before entering the Army the patient had had "poison ivy" which yielded promptly to treatment; otherwise, his skin had always been clear. He smoked about thirty cigarettes daily and drank six to eight cups of coffee. He had taken one atabrine tablet (0.1 Gm.) daily, six times a week for seven months.

The physical examination revealed a well developed but undernourished man in no distress. The scalp was hardened with tightly packed fine scales. A marked, patchy alopecia was present. The eyebrows had disappeared. The skin of the face as well as of the rest of the body was distorted by purplish, raised, irregular nodules 1 to 2 cm. in diameter. Coalescence had occurred to produce solid expanses over the forearms and thighs and net-like patterns over the trunk, arms and legs. The dorsal and lumbar spine areas were also involved, the extent of the lesions increasing from above, downward as far

as the belt line. Strands of reticulation sloped off to the sides giving the effect of a spruce tree pattern. The belt line was relatively free. There was fine scaling of all the lesions. Lichenification was marked about the neck, wrists and ankles. The palms and soles were undergoing patchy peeling. A number of the toe and fingernails were lifted by a subungual accumulation of hard granular material which was darkly pigmented. These nails were grooved and pitted. A single, annular, slightly raised violet lesion was found on the glans penis. There was generalized adenopathy and pitting edema of the ankles was present. The only other significant finding was marked pyorrhea.

The results of laboratory examinations were as follows: the red blood cell count 3,910,000; the hemoglobin 80 per cent; the white blood cell count 7,050 with polymorphonuclears 73 per cent, lymphocytes 25 per cent and eosinophiles 2 per cent. The sedimentation rate was 9 mm. in one hour. A urinalysis, the Kahn test, an x-ray film of the chest and an electrocardiogram were all normal.

TABLE I

THE DISTRIBUTION OF THE SIGNIFICANT PHYSICAL FINDINGS IN THE TEN CASES OF LICHEN PLANUS

| Lesions of the Skin | Case I | Case II | Case III | Case IV | Case V | Case VI | Case VII | Case VIII | Case IX | Case X |
|---|---|---|---|---|---|---|---|---|---|---|
| Physical Properties | | | | | | | | | | |
| Polygonal papules | + | ++ | +++ | 0 | ++ | ++ | + | 0 | + | + |
| Acuminate papules | +++ | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Umbilicated papules | 0 | + | ++ | 0 | 0 | 0 | 0 | 0 | 0 | ++ |
| Nodules | +++ | +++ | +++ | +++ | +++ | +++ | + | +++ | +++ | +++ |
| Violet or purple | +++ | +++ | +++ | +++ | +++ | +++ | +++ | +++ | +++ | +++ |
| Wickham's striae | +++ | +++ | +++ | 0 | ++ | ++ | 0 | +++ | 0 | 0 |
| Patterns | | | | | | | | | | |
| Reticulation | +++ | +++ | +++ | +++ | +++ | +++ | +++ | +++ | +++ | 0 |
| Solid expanses | +++ | +++ | +++ | +++ | +++ | ++ | +++ | ++ | + | 0 |
| Lichenification | +++ | +++ | +++ | +++ | +++ | ++ | +++ | ++ | +++ | 0 |
| Distribution | | | | | | | | | | |
| Lines of cleavage | + | + | ++ | + | + | + | +++ | + | + | 0 |
| Flexor surfaces | + | + | + | + | + | + | 0 | + | +++ | 0 |
| Nerve distribution | + | + | ++ | 0 | 0 | 0 | +++ | 0 | 0 | 0 |
| Generalized | +++ | +++ | +++ | +++ | 0 | 0 | +++ | 0 | 0 | 0 |
| Special Sites | | | | | | | | | | |
| Scalp | +++ | +++ | ++ | +++ | +++ | ++ | + | +++ | 0 | 0 |
| Eyelids | + | +++ | +++ | +++ | +++ | +++ | +++ | +++ | 0 | 0 |
| Palms | ++ | ++ | 0 | 0 | ++ | ++ | ++ | +++ | 0 | 0 |
| Fingernails | +++ | +++ | 0 | 0 | 0 | +++ | ++ | +++ | 0 | 0 |
| Soles | ++ | ++ | 0 | 0 | ++ | ++ | 0 | ++ | 0 | 0 |
| Toenails | +++ | +++ | 0 | 0 | 0 | +++ | 0 | 0 | 0 | 0 |
| Glans penis | + | ++ | 0 | 0 | 0 | 0 | 0 | 0 | 0 | + |
| Lesions of the Mucous Membranes of the Mouth | | | | | | | | | | |
| Buccal | 0 | +++ | 0 | 0 | ++ | 0 | 0 | ++ | ++ | 0 |
| Lingual | 0 | 0 | 0 | 0 | ++ | 0 | 0 | +++ | 0 | 0 |
| Labial | 0 | + | + | ++ | +++ | + | +++ | ++ | ++ | ++ |
| Other Features | | | | | | | | | | |
| Skin | | | | | | | | | | |
| Exfoliation | 0 | ++ | 0 | 0 | 0 | +++ | ++ | +++ | 0 | 0 |
| Secondary infection | 0 | 0 | +++ | 0 | 0 | 0 | ++ | 0 | 0 | 0 |
| Linear lesions | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | +++ | + |
| Bullous lesions | 0 | 0 | +++ | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Miscellaneous | | | | | | | | | | |
| Adenopathy | ++ | +++ | +++ | +++ | ++ | +++ | +++ | +++ | +++ | +++ |
| Ankle edema | ++ | +++ | +++ | +++ | 0 | + | +++ | +++ | 0 | 0 |

0 means Absent. + means Slight Degree. ++ means Moderate Degree. +++ means Marked Degree.

For medication the patient was given phenobarbital, ferrous sulfate and atabrine by mouth; an antipruritic lotion for general application and a sulfur salicylic acid ointment for the thickened areas of the skin as well as bismuth sub-salicylate in oil intramuscularly once a week. He was kept at rest much of the time and the use of tobacco and coffee was curtailed. Because of pyorrhea fifteen teeth were extracted and dental plates prepared.

The chart was normal throughout the patient's stay. New lesions appeared on the face, abdomen and feet as small violet nodules which grew larger and developed fine scales. The older purple lesions turned a greyish-brown color and in the course of three months flattened out. On April 8, 1944, two biopsies were performed. A week before evacuation the patient noticed that after bathing with soap and water his towel would grow dirtier the more he rubbed his skin. At the same time areas of light skin appeared where thickened and darkly pigmented expanses had existed. Needless to say, this turn in the course of events did a great deal to buoy the patient's spirits which had been periodically depressed. He left by plane for the United States on May 16, 1944.

*Pathological Report.** The specimen was taken from the anterior thigh and it contained a nodular, dark-purplish, slightly scaly lesion which was about two months old. Microscopically, there was moderate hyperkeratosis, hypertrophy of the epithelium and marked broadening and downgrowth of the rete pegs. The basement membrane appeared irregular because of thin streamers of cells which extended into the underlying corium. The latter was edematous and contained many new blood vessels, a heavy infiltration of lymphocytes and much coarse brown pigment.

The upper back was the site of this biopsy which included a patch of fine, papular lesions with central plugging and a dirty color. Microscopically, the epithelium was extensively pigmented. Its surface was irregular due to thickenings apparently associated with downgrowth of the rete pegs. Beneath these areas the corium showed increased vascularity, a slight amount of round cell infiltration and pigmentation.

This patient had the most marked skin involvement of any in the series; nevertheless, the blood studies and his symptomatology were not remarkable.

Case II. This thirty-three year old mechanic was admitted in March 17, 1944, because of a skin disorder which had involved his whole body for a period of a month.

On October 1, 1943, the patient arrived in New Guinea. About four months later January 12, 1944), he developed a reddish, dry, scaling patch on the inner aspect of the right thigh just above the knee. One week later both palms began to peel and at the same time red and scaling spots appeared on various parts of his body. They became raised and turned purplish. The involvement was most marked at points of irritation like the belt, collar lines and the shoulder tops. Itching at night was intense. Blisters broke out on a number of the nodules. Within several weeks the rash had become widespread and dependent edema was first noted.

The family history was negative for skin diseases but positive for allergy, in that two cousins and one uncle had suffered from hay fever. In the past the patient had had a few minor fungous infections between the toes and once in the crotch, all of which responded quickly to treatment. Otherwise his skin had always been clear and his health excellent. He had taken one atabrine tablet (0.1 Gm.) daily for five and one-half months without any untoward effect.

Upon physical examination the patient was found to be well developed but quite thin. Despite his affliction he was cheerful. The scalp was practically identical with that of the previous patient. He also had nodular unit lesions which coalesced into broad expanses with lichenification and elsewhere into reticular configurations. These lesions were of a bright, reddish-purple color and associated with a generalized diffuse violaceous erythema. Scaling was prominent, the individual scales being shiny, white, thin and large. There was spotty des-

* All the pathological reports in this article were prepared by Lieut. Col. Edward A. Birge, Medical Corps, Army of the United States.

quamation of the palms and soles. The nails were affected as was described in case I. The glans penis contained two nodules marked by fine whitish striae. The buccal mucous membrane showed both linear and annular, milky-white, raised lesions bilaterally. The annular ones were juxtaposed to large, gold, dental crowns. The lips presented a chapped appearance and areas of brown pigmentation not limited to the vermilion portion. The post-auricular, cervical, axillary, epitrochlear and inguinal glands were all enlarged but not tender. The lower edge of the liver was palpated two finger breadths below the costal margin. The ankles were markedly swollen with pitting edema.

The white blood cell count was 10,950 with polymorphonuclears 77 per cent and eosinophiles 6 per cent. The sedimentation rate was 11 mm. in one hour. Other routine tests were not remarkable. A serum protein determination as well as an x-ray film of the chest were both normal.

The patient was kept in bed and was given phenobarbital and bismuth subsalicylate in the buttocks at weekly intervals while mineral oil was administered to the skin. With rest in bed the edema gradually subsided but never disappeared. For about ten days he ran an afternoon fever as high as 102°F., without any symptoms other than feeling hot. There were no physical findings to explain the fever and the laboratory studies, including malaria smears, were negative. When the afternoon application of mineral oil to the whole body was stopped the fever promptly subsided. On April 14, 1944, two skin specimens were removed surgically. During the six week period of hospitalization there was no significant change in the dermatological condition. He departed for the United States on May 1, 1944.

*Pathological Report.* The specimen came from the anterior chest and represented a section of a strand in the so-called "reticular pattern." Clinically, the lesion was raised, reddish-purple and scaling. It was considered to be about two and one-half months old.

Microscopically, the epithelium was thin and edematous. Moderate hyperkeratosis was present. Little remained of the rete pegs except a few thin columns of cells. The corium was vascularized and infiltrated by many lymphocytes and it revealed a moderate amount of fine brown pigment lying in macrophages. There was some inflammatory reaction around the hair shafts and sweat glands in the section. The lesion from the thigh had been present for about three months. It was nodular, raised, rough, and purple. The so-called "broad expanses" were made up of such units.

Microscopically, hyperkeratosis was marked. The epithelium was heaped into thin, irregular papillary folds giving the appearance of a verruca. There was an associated, irregular downgrowth and broadening of the rete pegs. The papillae of the corium were edematous; they were also highly vascularized and infiltrated by numerous lymphocytes. A moderate amount of coarse, brown pigment lay free in the interstices of the corium as well as inside macrophages. A little of this pigment was seen in the epithelium.

This was the only patient with fever of obscure origin. The relationship between the fever and the general application of mineral oil appeared to have been satisfactorily established.

CASE III. A tank gunner, nineteen years of age, came into the hospital as a litter case on March 21, 1944, complaining of skin trouble lasting for five months and which had become generalized ten days before admission.

When eight years old the patient had scarlet fever and at that time white spots had developed on various parts of his body, including the eyelids, and had never disappeared. In October, 1943, the patient landed on Goodenough Island and subsequently went to Cape Gloucester on New Britain. After a few weeks of exposure to the tropical sun, the upper eyelids became sunburned and highly irritated. Similar white patches on his bare arms were next involved; finally, those on his trunk and legs also became red, dry, scaly and tender even though covered by clothing. Unlike an ordinary sunburn the condition did not clear. About January 15, 1944, oval and round spots of the same kind developed on the normal skin, especially on the legs. These areas were raised, "maroon" in

color and extremely itchy. He felt well and kept at his job.

Various lotions and ointments were prescribed at the dispensary but none proved effective; therefore, he was admitted to the nearest hospital and in the early part of March was given a series of epsom salt baths. After the third treatment, his "whole skin broke out" and he grew too sick to take much notice of the types of lesions. He was evacuated by plane.

No member of his family was known to have had skin or allergic diseases of any kind. Except for the vitiligo the patient had never had any skin disease nor had he ever suffered from hives, hay fever or asthma. He had taken atabrine daily for six months in 0.1 Gm. doses without difficulty.

On physical examination the patient appeared undernourished, acutely ill, weak and uncomfortable. The outstanding skin lesions were upon his chest, back and legs and were manifested by a dense, nodular eruption with coalescing ulcerations whose bases were covered with purulent discharge. Elsewhere, polygonal and umbilicated papules, nodules with striae and other features listed in Table I were present. The neck, antecubital and popliteal areas oozed moderately. Several bullae were found superimposed on nodular elements, one over a shoulder blade being about 1 inch long and sausage-shaped. The back showed a solid expanse of involvement with the spruce tree effect. The entire belt line was relatively free. There was a mild, patchy alopecia with slight scaling of the scalp. The vermilion portions of the lips contained pigmented spots. Verrucous plaques were prominent over the buttocks and thighs and the ankles were swollen with pitting edema.

The laboratory studies revealed: red blood cell count 4,960,000; hemoglobin 65 per cent; white blood cell count 14,050 with stabs 14 per cent, segments 70 per cent, lymphocytes 7 per cent, monocytes 3 per cent, eosinophiles 5 per cent and basophiles 1 per cent. The urinalysis and Kahn tests were negative. A sedimentation rate was 40 mm. in one hour.

Treatment consisted of bed rest, colloidal baths, boric acid compresses to the eyes and ears and alibour solution compresses to the ulcerated lesions followed by cod liver oil dressings. The response was excellent. As the infected areas cleared within the first week, the fever which had persisted around 101°F., gradually subsided. On the twelfth day the sedimentation rate had fallen to 21 mm. per hour; thereupon, bismuth injections were started on a weekly basis. As the acute dermatitis subsided, the patches of vitiligo could be discerned over the eyelids, arms, trunk, genitalia and legs. They varied in diameter from 1 to 3 inches. The lichen planus reticular strands of nodules in these depigmented areas were the most distinctly violet colored of any in this series of cases. Whereas, those lesions in the adjoining normal skin assumed a darker purplish hue and later turned brownish. Biopsies were taken of the different types on April 8, 1944. At the time of transfer on April 28, 1944, considerable improvement was evident, especially about the eyes and over the trunk. The ankle edema had disappeared and the patient was well on his way to regaining the 36 pounds he had lost.

*Pathological Report.* This specimen was excised from the abdominal wall where reticulation involved both normal and depigmented skin. The lesion was violet, raised and finely scaling. It had been evolving for approximately two and one-half months.

Microscopically, there was moderate hyperkeratosis. The rete pegs showed an irregular broadening and downgrowth and a few small epithelial pearls were found in them. The epithelium between the pegs was thin and atrophic. At one place a tendency toward the formation of verrucous papillae was evident. The corium was infiltrated by large numbers of lymphocytes and a few eosinophiles. New blood vessels were also prominent, especially just beneath the epithelium and about the hair follicles; in addition, small amounts of brown pigment were present.

A skin nodule was excised from the anterior chest. This lesion was umbilicated, covered with fine scales and colored violet. In one segment it gave a pseudopod-like offshoot which was considered indicative of the manner in which reticulation is produced. The histologic picture was the same as described for the specimen obtained from the abdominal wall, except that the papillary downgrowth was more striking.

No histopathological difference was noted between the lichen planus lesions of the normal skin and those of the vitiligo patches.

CASE IV. A thirty year old, military policeman was admitted on April 25, 1944, because of generalized skin disease. He had been in New Guinea for eight months. Six months before admission he developed a vesicular rash on the volar aspect of both forearms which was attributed to a certain red sap from trees he had been handling in building a mess hall. Under treatment with merthiolate the eruption disappeared in six days.

Four months before admission the dorsa of his feet and toes began to itch. Calamine lotion afforded relief. Subsequently, the pruritus involved the rest of the legs and soon spread over his entire body. There was no rash. At the same time he developed three dime-sized sores on the lower lip which were painful, raw and oozing. Crusts formed, and the lip became swollen. After two months of various kinds of topical applications the lesions healed.

Approximately two months before admission his arms, legs and eyelids became sunburned. Contrary to previous experience the affected skin became unduly red and swollen. In ten days it began to scale. This process then extended over the whole body and became complicated by red blotches the size of dimes, quarters and half-dollars. These spots were raised over the dorsa of the arms and the itching became more intense and interfered with sleep. The blotches tended to coalesce and in the region of the knees they became covered with blisters. The latter broke and formed "sores with pus." Elsewhere, similar ulcerations developed as scaling occurred, being most marked over points of pressure such as the hips and elbows. The patient stated that scratching produced blisters the size and shape of his little finger. His ankles and lower legs became swollen.

During the month before coming to this hospital he was given various kinds of treatment, the most helpful of which was boric acid soaks. This promoted a "shedding of skin, scales and crusts," which left a bright red, clean delicate surface. The latter promptly "dried out, scaled up and formed small bumps."

The family and past histories were negative for allergic and skin diseases, except that the patient had had mild evidences of "athlete's foot" which always responded quickly to common disinfectants. In October, 1943, he suffered an attack of dysentery and in December an attack of malaria. The latter recurred about one month before admission. He had taken atabrine regularly as a suppressive measure and the same drug was used therapeutically on both occasions.

The patient was a well developed and well nourished soldier in no distress. He presented a widespread violaceous erythema, nodular reticulation with scaling and solid expanses of thickened, rough, plaque-like lesions with a greenish-grey surface. The latter were distributed over the lumbar and gluteal areas, the extensor aspects of the elbows and knees and over the ankles. There was pronounced, diffuse alopecia and loss of pubic hair. The eyelids were lichenified. The lips were diffusely pigmented and they showed lacy, bluish-white striae. The ventral part of the belt line was relatively uninvolved. Other positive and negative findings are indicated in Table I.

The urine was normal and the Kahn tests were negative. The red blood cell count was 4,800,000 and the hemoglobin 14 Gm. The white blood cell count was 13,900 with 66 per cent polymorphonuclears and 15 per cent eosinophiles. The sedimentation rate was 11 mm. in one hour and the serum proteins totaled 5.2 Gm. per cent. The clinical chart was normal.

The patient was given a course of penicillin therapy: 20,000 units intramuscularly every three hours for eight and one-half days. No significant change of any kind was observed; therefore, the measure was abandoned and bismuth injections were begun. Local applications of mineral oil kept the skin pliable and seemed to cut down the tendency to scale. On May 9, 1944, a skin lesion was biopsied. When he departed for the United States on May 15, 1944, the eyelids had shown the most improvement. The nodular elements remained about the same throughout his stay in the hospital.

*Pathological Report.* The abdominal wall was the site of this biopsy. The skin in this region showed violaceous erythema, scaling and thickened strands arranged in net-like patterns.

Microscopically, the epithelium showed adjoining areas of hypertrophy and atrophy. In the latter, the epithelium was represented merely by a thickened layer of keratin and a few, very thin lines of basal cells. The hypertrophied portion revealed definite hyperkeratosis. The rete pegs were broad and thick and from them, thin streamers of cells stretched out into the corium. The corium was extensively vascularized and infiltrated by lymphocytes with an occasional eosinophile. The inflammatory process was restricted to the region immediately beneath the epithelium, although some extension was noted along a hair shaft which was included in the section. No increase in pigmentation was observed.

The course of penicillin therapy was tried empirically. Since the lesions of lichen planus were in no way changed, this medication was not used further.

Case v. This twenty-five year old infantryman came into the hospital on March 31, 1944, complaining of a generalized skin disease which had started six weeks previous to admission.

In December, 1943, he had gone to New Guinea and after about one month he began feeling below par and started losing weight. In mid-February, 1944, red, itching blotches appeared on his palms and soles without any known provocation. Similar lesions soon developed on his arms and legs and spread rapidly over his whole body. The eyelids, nose and lips were early involved by inflammation and dryness accompanied by burning and itching. This was followed by oozing and crusting. He was first hospitalized on March 24th and was evacuated south by airplane.

The family history and the past personal history were negative for allergy and skin disease. He had taken atabrine regularly for four months without any difficulties. Physically the patient was poorly nourished and weak. His morale, however, was good. An outstanding feature was the marked degree of sanguineous crusting of the lips and nose; the latter was entirely and solidly encased in a dark-reddish, scab-like formation which was thick and closely adherent. The upper and lower eyelids were similarly affected although to a milder degree. The palms and soles showed a patchy peeling and the limb and trunk lesions were lightly scaling. The other findings are scored in Table 1.

A complete blood count and urinalysis were normal. A Kahn test and a malaria smear were both negative. The chart was flat. The patient weighed about 120 pounds whereas his normal weight was 135 pounds. Treatment was primarily directed toward improving his general condition by diet and rest. Without sedation he slept most of the time during the first ten days. The crusts had to be soaked for five or six days before they loosened sufficiently to be removed. On April 8, 1944, two biopsies were done. Bismuth injections were begun before his departure on May 1, 1944.

*Pathological Report.* This specimen, which was removed from the right upper arm, consisted of a patch of discrete, violet papules with central plugging. The sections showed moderate hyperkeratosis and a tendency of the epithelium to form tiny, verrucous papillae. The rete pegs had enlarged in irregular fashion both downwards and to the sides. One small area of hemorrhage was found in the epithelium. The corium was filled with round cells and new capillaries to which was added a small amount of brown pigment.

The second preparation was a hypertrophic nodule with fine scaling and a violet color which had been developing for about six weeks on the volar aspect of the left forearm. The description for the first specimen applied to this specimen as well, except that the hypertrophy of the rete pegs in the second specimen was more marked and more brown pigment was present.

Case vi. A forty-one year old orderly entered the hospital on February 7, 1944, with a generalized eruption of several weeks' duration.

He had arrived in New Guinea in August, 1943, feeling well; however, after a few weeks he lost his appetite for no known reason. By the first of January, 1944, his weight had dropped from 145 pounds to 130 pounds and he felt weak. About January 10, 1944, after using a broom in routine fashion, he developed a large blister on his right palm. This had never happened before. Within a day or two the dorsa of both hands grew red and scaly but not itchy. There had been

no known exposure to any irritant. The affected skin proceeded to peel. Potassium permanganate soaks were prescribed at the dispensary and used three times a day for three weeks. After the first few times the rawness and scaling extended up the arms and appeared on the legs and within a few days the whole body was involved and he became acutely ill.

The family history was non-contributory. Except for mild and intermittent "athlete's foot," the past history was negative for skin diseases. He had never had hay fever, hives or asthma. The daily taking of one atabrine tablet for six months before admission had never upset him.

The physical examination revealed a well developed but emaciated soldier who weighed about 105 pounds, whereas his normal weight was 160 pounds. The entire integument was scaling in large flakes and exhibited a diffuse violet erythema. Over the shins, upper trunk and arms were dark purple nodules which had coalesced into solid expanses as well as reticular patterns. A number of polygonal papules were found about the eyes and the fingernails and toenails were the most affected of any of the patients in the series. The majority had been so raised by pigmented material beneath the nails that as the matter crumbled away the nails themselves were left quite detached. Patchy alopecia and pigment changes in the lips were also noteworthy.

The most significant laboratory finding was a white blood cell count of 9,850, with 36 per cent eosinophiles. This was checked the next day at 11,300 and 24 per cent, respectively. The urine and Kahn tests were negative while an x-ray examination of the chest was normal. Low grade fever was present.

The patient was kept at absolute bed rest and was fed as much food as he could tolerate which was supplemented by polyvitamin capsules. Mineral oil proved the most satisfactory unction for the skin. Itching was of little consequence and on February 10, 1944, a skin biopsy was performed. Improvement was slow, desquamation continuing actively for nearly five weeks. The eosinophile count fell to normal limits. A sedimentation rate on March 18, 1944, was 12 mm. in one hour. Not until exfoliation had practically stopped did he begin to gain weight, although his appetite had been excellent throughout his stay in the hospital. When evacuated on April 29, 1944, he weighed 125 pounds, his face was well cleared and the purple nodules were generally flatter and more discrete while those on the legs showed fine whitish stippling.

*Pathological Report.* The biopsy site was the right shin where a purple nodule was excised from a "solid expanse." According to the history the lesion was about three weeks old. The clinical picture was complicated by an associated exfoliative dermatitis.

On microscopic examination there was marked thickening of the epithelium and hyperkeratosis. The rete pegs extended broadly and deeply. Hyperpigmentation was noteworthy. A massive infiltration of lymphocytes involved the upper portion of the corium. No eosinophiles nor leukocytes were found; in general, the corium was well supplied with new blood vessels.

It is interesting, that despite the high level of eosinophiles in the blood, none was found in the inflammatory infiltration of the corium.

Case VII. A thirty-seven year old able-bodied seaman entered the hospital on May 28, 1944, complaining of a rash which had appeared one month previous to admission.

The patient stated that at the age of fourteen he had had a spotty eruption over the neck, arms, buttocks and legs which was diagnosed by a skin specialist as lichen planus. Without any treatment that he could recall the condition cleared entirely in a matter of six or eight months.

During the following twenty-three years the patient suffered no skin disease whatever. Toward the end of January, 1944, his ship took him to the New Guinea area but despite the intense heat he felt very well. Since he wore only shorts and shoes a general coat of tan was soon acquired. Approximately two months before admission, however, an old scar on his left shin began to crack, scale and turn red. The spot quickly enlarged and a similar process started on the other leg. After several weeks both areas became infected; thereupon, sulfanilamide powder was applied daily.

One month prior to entry both palms and the sides and backs of most of his fingers became dry, cracked and rough with scales. Soon, tiny "pimples" appeared on the backs of the hands and spread up the arms and across the shoulders and neck. No further treatment was given before he was evacuated to this hospital.

The family history was non-contributory. The past history was noteworthy for revealing a duodenal ulcer which had been proven by x-ray examination four years previously. Meanwhile he had controlled his symptoms satisfactorily with amphojel. At certain times of the year he suffered mild attacks of hay fever, the cause of which was never determined. During his service in the islands he took atabrine regularly without experiencing difficulty. He had not handled possible irritants, as for example, gasoline or brush but he admitted having developed "athlete's foot" just before his present illness. He had had a "chest cold" for approximately a week's time.

The positive physical findings were limited to the skin and chest. A shallow ulcer measuring 2 by 2½ inches and showing signs of pyogenic infection was present over the left shin. There was a similar but smaller one on the right shin. A fine papulopustular eruption with inflammation extended over the arms, shoulders, neck and to a lesser degree the legs. The skin of the backs of the hands and of the neck was thickened and lichenified. The palms showed patchy peeling. There was mild scaling and cracking between several toes. Increased voice transmission was found anteriorly over the third right interspace.

The laboratory examination revealed a temperature of 102°F., pulse 88 and respirations 20, as well as a normal urine and negative Kahn tests. The red blood cell count was 4,520,000; hemoglobin 14 Gm.; the white blood cell count 11,300 with polymorphonuclears 76.5 per cent, lymphocytes 12 per cent, monocytes 6.5 per cent and eosinophiles 5 per cent. A sedimentation rate was 40 mm. in an hour. An x-ray film of the chest revealed signs of patchy pneumonia in both upper lobes.

With complete bed rest, symptomatic treatment and wet boric acid compresses to the ulcers the temperature returned to normal by lysis within eight days. Repeated examinations of the sputum and gastric contents on direct smear after concentration as well as on culture were negative for acid-fast bacilli. A second strength tuberculin test was positive. During the first three weeks the chest signs and symptoms subsided, the sedimentation rate fell to 18 mm. and the white blood count fell to 7,750. The eosinophiles, however, rose to 12 per cent. By that time the pustular elements had disappeared leaving a dermatitis marked by bright purplish erythema, deeply purple lesions forming net-like patterns scaling and surrounding lichenification. The back down to the waist, the eyelids and surrounding skin as well as the scalp just above the ears had also become involved. Other features may be noted in Table 1.

Injections of bismuth were started on June 26, 1944, and were given once a week throughout his hospital stay. Chest x-rays taken at weekly intervals showed a gradual and satisfactory clearing of the pulmonic areas of density. A final diagnosis of primary atypical pneumonia was made. On July 17, 1944, the indolent ulcer on the left shin was covered by a skin graft, the end result of which was excellent. The eosinophile level fell to 3 per cent. A skin biopsy of an isolated, slightly nodular lesion was taken from below the right clavicle on August 9, 1944.

When the patient was evacuated on August 22, 1944, his general condition was very good and his skin exhibited definite signs of improvement. No raised lesions remained. Scaling had largely ceased, leaving brown pigmented skin of normal texture. This was particularly noticeable about the sacral, gluteal and ocular regions. Lichenification had regressed in all quarters and the purple hue had grown dull and brownish.

*Pathological Report.* It is estimated that the skin lesion of the chest appeared approximately three months before this biopsy was performed. Microscopically, the epithelium was generally of normal thickness with slight hyperkeratosis, except for one segment which showed extreme atrophy and parakeratosis. The rete pegs had sent small prolongations into the corium while the papillae were packed with lymphocytes and large endothelial cells. The corium contained a moderate amount of golden yellow pigment.

CASE VIII. When admitted to the hospital on March 29, 1944, this forty-one year old marine's chief complaint was a generalized scaling of the skin. He had spent five months on Guadalcanal, nine months in South Australia and finally six months in New Guinea. Ten weeks before admission both index fingers broke out with an eruption of small blisters. The dorsa of the feet and the ears soon developed the same condition. One week later a raised, red, well defined lesion developed on the right anterior chest at the costal margin. Gentian violet was applied to all the involved areas and within a few hours the ears, hands and feet became swollen and greatly irritated. Ten days later (about seven weeks before admission) "good sized bumps came out all over the skin." Thereupon, generalized scaling began including peeling of the palms and soles. Four weeks before entry he developed a fever of 101°F. Examinations of the blood for malaria and the stools for ova and parasites were negative. The white blood cell count was 14,150 with 28 per cent eosinophiles.

The family history and the past history were negative for allergy and skin diseases. In 1936, the patient contracted syphilis and received intravenous and intramuscular treatments regularly for the next two years. There was no associated rash. Despite the alleged consistent taking of atabrine while on the islands, he suffered two attacks of malaria on Guadalcanal and one in New Guinea. Treatment on those occasions with atabrine apparently caused no untoward effects.

The patient's build and nutritional aspects appeared normal. From head to toe his skin was desquamating with large scales and showed a general, diffuse, violet-tinged erythema. The largest nodule found was the one previously mentioned on the right chest. It was raised, well defined, oval, 1.5 cm. in length, violet and exhibited Wickham's striae. On April 8, 1944, this lesion was removed surgically for histological study. Similar although smaller, nodules were present over the backs of the hands, fingers and arms and on the trunk. Because the legs were most affected by the exfoliative process, it was difficult to determine the existence of nodules. The buccal mucosa and lips showed milk white, lacy lesions and the tongue showed irregular, large, white plaques.

The laboratory studies revealed no anemia. A white blood cell count was 10,900 with 60 per cent polymorphonuclears and 18 per cent eosinophiles. Both the Kahn test and the urinalysis test were normal. A sedimentation rate was 26 mm. in one hour.

Treatment consisted of rest in bed, phenobarbital, colloidal baths, soothing lotions, atabrine in daily doses of 0.1 Gm. and weekly injections of bismuth subsalicylate.

For the first ten days he had an afternoon fever of about 99.4°F. Gradually the scaling and peeling diminished from above, downward. Finally, nodules could be detected on the legs in solid and reticular configurations. The ankle edema subsided but had not disappeared when he was transferred on May 1, 1944.

*Pathological Report.* The clinical aspects of the specimen have been discussed above. The lesion had been present for about two and one-half months. Histologically, the rete pegs of the epithelium were hypertrophied and completely surrounded by granulation tissue. The latter was heavily infiltrated with lymphocytes and a few leukocytes.

CASE IX. This soldier, a thirty-six year old cook, was admitted on March 7, 1944, because of skin lesions which had been developing for several months.

The patient landed in New Guinea in July, 1943, and had enjoyed good health until January, 1944. Early in that month he noticed an oval, red, raised, slightly itchy spot beneath his wrist watch strap on the volar surface. Within one month similar lesions spread over the forearm and appeared on the other arm. All units increased in size and tended to run together. In mid-February, 1944, the same process began on the inner aspect of the left ankle and extended up the leg; the right leg next followed suit. Finally, lesions developed at the base of the neck and over the upper anterior chest. During those weeks he observed an occasional blister on normal appearing skin.

The family and past histories were negative for dermatological, allergic and nervous diseases. He had taken atabrine regularly for eight months without any difficulty.

The patient was found to be high-strung, well developed, well nourished and in no discomfort. The lesions were most conspicuous on the flexor surfaces of the arms and medial aspects of the legs. White papules were present inside the corners of the mouth and white, lacy lesions were noteworthy on the lips. Besides a grouping of lesions along the lines of cleavage at the base of the neck, there were several distinctly linear lesions, 6 inches long and running down over the upper chest, more or less in line with his dog tag chain. Below the right shoulder blade, a circular lesion was found which measured 1 cm. in diameter, it was depressed and depigmented and showed a slightly violaceous areola.

The laboratory tests gave the following results: white blood cell count 9,750; eosinophiles 4 per cent; polymorphonuclears 71 per cent; urine and Kahn tests were negative and the sedimentation rate was 19 mm. in one hour. An x-ray film of the chest was normal.

The patient was given phenobarbital by mouth, a sulfur salicylic acid ointment to the lichenified and nodular expanses and a course of bismuth sub-salicylate injections.

Under observation the chart remained normal throughout his hospital stay. Small, violet nodular lesions developed to a minor extent over the dorsa of the feet. Two biopsies were performed on April 8, 1944. Before evacuation on May 16, 1944, the eruption about the neck had cleared the most of all. The purplish nodular elements had regressed considerably and assumed a brownish tinge. A marked bismuth line had developed in the gums without any symptoms. The labial and buccal lesions remained static.

*Pathological Report.* This specimen contained the lesion below the right shoulder blade which was described among the physical findings. It looked as though it might have been an old atrophied nodule.

Microscopically, there was moderate hyperkeratosis. The epithelium was thin and showed a slight tendency to verrucous formation. The rete pegs had been largely flattened. The corium was normal except for a few small areas of lymphocytic infiltration and a slight increase in vascularity. Very little brown pigment was present.

This second biopsy was from the lateral aspect of the right leg where nodular lesions had been progressing for about six weeks. A segment of a reticulation strand was selected which had passed through the violet and purple stages and had become quite brown. The microscope revealed marked hyperkeratosis with considerable blood present among the keratin layers. The epithelium was greatly hypertrophied including the rete pegs. The Malpighian layer appeared frayed where individual cells had separated off into the underlying corium. Inflammatory changes were present about the rete pegs and the sweat glands. Only a little brown pigment was found in some cells of the corium.

Case x. A twenty-six year old cook was admitted on August 5, 1944, because of a widespread skin disorder of nine months' duration. The patient had been at the same base in northern Australia for the entire fourteen months of his overseas duty. In November, 1943, he noticed that a "heat rash" across his shoulder blades was behaving in an unusual manner. For years his skin had been prone to break out with tiny blisters whenever exposed to considerable heat and as a result there would be extreme itching. He would scratch and thus rupture the lesions which would proceed to dry up and disappear. The prodromal stage of the present illness is dated from the time (November, 1943) when the drying was first followed by residual, reddish, raised spots which were scaling. In the course of a week they turned purplish and in two more weeks became flat and smooth; finally, only white dots were left.

He attributed the eruption on his back to working in the sun without a shirt. Soon similar rashes appeared on the anterior chest, the arms and to a slight degree on his legs. There was no question in his mind but that the lesions were due to the steam heat from the mess kit cleaning drums over which he worked. On his days off, no eruption occurred even though he took sun baths and as he attained a coat of tan the incidence of the heat rash seemed lowered.

Four months before admission he was put to work at a field kitchen unit where the fire box was just off the ground. "The heat hit my legs through my pants just like pins and needles,"

he said. The individual blisters at those sites came out about three times their former size and the resulting purplish "bumps" began to run together. Trunk and arm lesions also became more marked. He thought his crotch region was spared because he wore shorts. Finally, the itching interfered with his sleep to such a degree that he reported on sick call and he was promptly sent to this hospital.

The histories of his mother, father, eleven siblings and relatives were negative for dermatological and allergic diseases. For many years the patient had "broken out all over with red spots" upon eating fifteen to twenty tomatoes in a day. He recalls no associated pruritus. While working on the family farm he had had similar eruptions intermittently over his extremities and chest which he called the "muck itch," supposedly due to dust, dirt and sweat. He never smoked excessively and had taken no atabrine or other drugs.

On physical examination the patient was found to be well developed and well nourished. Polygonal, shiny, flat topped papules of violet color were scattered generally over the arms, legs and trunk. They varied from pinhead size to three times larger. Many umbilicated papules were also present. The lesions tended to be grouped in patches, for instance over the shoulder blades, deltoid and parasacral regions. Excoriations were numerous and linear alignment of papules was noted repeatedly. On the extensor and lateral aspects of the legs the unit lesions had apparently coalesced into larger nodules. Scaling was most prominent there. The lower lip contained ramifying whitish striae. The axillary, epitrochlear and inguinal glands were slightly enlarged but not tender. The only other abnormality was the absence of knee jerks.

The results of the laboratory examination were as follows: The hemoglobin was 15.9 Gm; the white blood cell count was 10,800 with polymorphonuclears 61 per cent, lymphocytes 31 per cent, monocytes 4 per cent, eosionophiles 3 per cent and basophiles 1 per cent. The sedimentation rate was 8 mm. an hour while the Kahn and urine tests were negative.

Intramuscular bismuth was started at once and was repeated four times at four day intervals. Thereafter, injections were given once a week. The dose was 2 cc. of subsalicylate in oil. Calamine lotion with 1 per cent phenol was used to relieve the itching.

On August 9, 1944, one skin specimen was excised from the upper abdomen and another from the right leg. Throughout the first three weeks of observation new lesions appeared every few days in widely scattered locations. For instance, one day a patch of typical papules broke out on the volar aspect of the right wrist. Two days later a palm-sized group of violet papulovesicles erupted over the lumboscaral region. Itching was intense and the tops of the eruptions were soon scratched off. The remaining papules became polygonal with shiny flat tops. The next day a 3 inch scratch mark was noted high on the right flank. Careful scrutiny revealed that it consisted of tiny papules in perfect alignment. The nodular lesions on the legs gradually regressed so that reticulation never developed. The patient was evacuated to the United States on September 1, 1944.

*Pathological Report.* The first specimen was taken from the upper abdomen and it contained small, polygonal, flat-topped violaceous papules. Microscopically, the epithelium appeared normal. The Malpighian cells were filled with pigment and there was minimal round cell infiltration around some of the small vessels in the corium.

The second biopsy from the leg included a purplish, scaling nodule which had begun as a vesicular lesion about four months previously. The sections showed increased thickness of the epithelium with marked hyperkeratosis. The rete pegs extended downwards in slender columns of cells. The epithelium contained several vesicles, in one of which were threads of fibrin plus a few monocytes. The corium was vascularized and filled with lymphocytes and a small amount of brown pigment was present.

## COMMENTS

Since the cause of lichen planus is unknown and since these cases were so strikingly similar in their signs and histories, it was hoped that some understanding of the fundamental nature of the disease might be

derived from this study. The microscopic examinations added nothing to what is already well known about the pathological picture of lichen planus. A number of the sections were stained with Prussian blue. Failure of the pigment to take the stain indicated the absence of iron. Although the case reports do not indicate it, dietary histories were taken but no significant deficiencies were encountered. No important evidence to indicate an allergic mechanism was forthcoming and in no instance was there an apparent association between the onset of the illness and primary skin infection by either fungi or bacteria. There was no reason to suspect that the disease might be contagious.

Certain features, however, do stand out from the mass of data presented in the case reports and they have been set down in Table II. The patients were for the most part in an older rather than a younger age group. Their past histories were not remarkable except that the patient discussed in Case VII had previously sustained a similar eruption. All but one had lived for months in the tropical islands north of Australia and had taken doses of atabrine. The disease characteristically came on insidiously with various kinds of pro-

TABLE II

SOME POINTS OF CLINICAL NOTE FROM THE HISTORIES OF THE TEN CASES OF LICHEN PLANUS

| Case | Age | Past History of the Skin | Features of the Period Immediately Preceding the Onset of the Present Illness | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Suppressive atabrine therapy, in months | Time spent in islands north of Australia, in months | Length of the prodromal stage, in weeks | Prodromal Signs and Symptoms | Possible Precipitating Factors | | |
| | | | | | | | Sun | Heat | Friction |
| I | 42 | Several minor attacks of poison ivy | 6 | 6 | 12 | Itching, vesicular eruptions over the volar aspects of the wrists and over inner thighs | .. | + | |
| II | 33 | Mild intermittent athlete's foot | 4½ | 4 | 2½ | Itching, scaling, red spots starting on the inner thigh; also, peeling of the palms | .. | + | + |
| III | 19 | Vitiligo | 4 | 3½ | 10 | "Sunburn" of the depigmented patches, including those covered by clothing | + | + | |
| IV | 30 | Mild intermittent athlete's foot | 6 | 6 | 16 | Vesicular rash on forearms for six days. Generalized itching. Sores on the lip | + | + | |
| V | 25 | Negative | 2 | 2 | 4 | Felt below par and lost weight | .. | + | |
| VI | 41 | Mild intermittent athlete's foot | 5½ | 5 | 14 | Felt below par and lost weight | .. | + | + |
| VII | 37 | Extensive "lichen planus" at the age of fourteen | 3 | 3 | 4 | Dryness and scaling of a scar on the left shin, followed by infection | + | + | |
| VIII | 41 | Negative | 4 | 3½ | 1 | Vesicular eruption on index fingers, feet, and ears | .. | + | |
| IX | 36 | Negative | 7 | 7 | 4 | Itchy, dry, red spot under wrist watch strap | .. | + | + |
| X | 26 | "Muck itch" from dirt and sweat. "Hives" from tomatoes | None | None | 20 | Vesicular eruptions leaving scaling, reddish spots | + | + | |

dromata. Irritation by physical agents seemed to be a common denominator in the pathogenesis; for example, trivial trauma incurred by using a broom in his routine work produced the initial lesion in Case VI. The wearing of a wrist watch strap set off the overt disease in Case IX. The precipitating factor in Cases III, IV, VII and X was probably sunburn.

It is impossible to draw any telling conclusions from the material at hand. Nevertheless, the author has a strong impression that the cause of this disease is intimately associated with the effects of climate on a peculiarly sensitive skin. What the sensitizing principle or principles might be, is (in the light of present evidence) so highly speculative that the matter will not be discussed herein.

## SUMMARY

1. Ten unusual cases of lichen planus which developed in the Southwest Pacific Area are herewith presented.

2. The term "lichen planus hypertrophicus, retiformis" is suggested as a proper diagnosis for the first nine cases.

3. Though the cause of this disease remains obscure, the present study suggests that climate plus individual (constitutional) susceptibility may be of basic importance in the pathogenesis. Suspicions as to possible sensitizing factors are considered too speculative to mention. Irritation by external physical agents apparently constitutes an important precipitating factor in the disease process.

## ADDENDUM

This paper was completed in the above form in September, 1944, at a time when it would have been highly undesirable to say that atabrine was strongly suspected as a major factor in the cause of atypical lichen planus. Even if atabrine had early been proven as the sole cause of atypical lichen planus, its continued use on a grand scale would have been justified since the malarial problem was so tremendous and the dermatological aspect so relatively minute. The incidence of this skin disease was approximately 2 per 1,000 per annum in the Pacific Ocean area.

It will be noted in the text and Table II that nine of the ten patients had taken small doses of atabrine regularly over long periods before signs of lichen planus appeared. This is, of course, compelling evidence for the theory that sensitization to the drug was produced and that the skin and mucous membranes were the reacting tissues, but why did characteristic lesions develop in Case X in the absence of the atabrine factor? The author knows of another case similar to Case X which occurred in the Assam-Burma region. Furthermore, some cases of atypical lichen planus improve, despite the continued use of atabrine, while others fail to improve for weeks or months after atabrine has been terminated. A final point which also casts doubt on the all importance of atabrine is the fact that relatively few cases developed in certain tropical areas even though the exhibition of atabrine was being carried out in the accepted manner. The vast majority of the atypical lichen planus cases occurred in rather restricted geographic regions, especially New Guinea, the Phillipines and the Assam-Burma border. The conclusion seems inescapable that other important factors besides atabrine must be carefully studied before the etiology of this disease can be established.

For further discussion see the article by Livingood and Dieuaide.[2]

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# Review

## Neurogenic Pain Simulating Visceral Disease*

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SINCE all pain from whatever origin is reflected through the nervous system, it follows logically that abnormal conditions primarily affecting some part of the nervous system could produce pain of a character and distribution that could closely simulate the pain of visceral disease. However, it is apparent that this fact is frequently lost sight of by the medical profession, and we have observed that this leads to therapeutic sins both of omission and commission.

While neurogenic pain can assume any clinical type, we frequently have referred to us as diagnostic and therapeutic problems patients who present pain syndromes which in character and distribution strongly suggest visceral disease as the cause. The most common of these are arm and chest pains simulating cardiac pain, abdominal pain simulating cholecystic or gastrointestinal disease and loin and back pain simulating urinary tract lesions. While sciatic pain with low back pain does not simulate visceral disease, it will be included in this group because it has the same pathogenic factors and because it has been generally considered a "medical" disease, leading to the too frequent erroneous conception that it should be attacked with various drugs, injections of the nerve trunk, removal of teeth and tonsils as supposed focal infections, and occasionally ill advised major surgical procedures if the patient be a female.

### CLINICAL TYPES

1. *Chest and Arm Pain.* In our experience this type of pain is seen most frequently on the left side. This is probably due to the fact that a mild degree of pain occurring in the left chest arouses anxiety which if present on the right would not be associated with the idea of heart disease and would not cause the patient to consult a physician. This type of pain is seen in all degrees of severity from mild, and sufficient only to arouse the patient's anxiety concerning his heart, to severe pain of sudden onset very closely simulating acute coronary thrombosis. Its location may be vaguely in the left chest with some radiation to the shoulder and left arm, or it may have a definite location in the precordium with radiation to the left arm and hand. The clinical picture of cardiac pain may be simulated so closely that even one who has had extensive clinical experience has difficulty in reaching a satisfactory decision regarding the exact nature of the trouble. If the electrocardiographic tracing is normal, some difficulty is encountered in satisfactorily diagnosing the trouble; but the difficulties are greatly increased if there are abnormalities in the electrocardiogram coexisting with neurogenic pain. Proper solution of the situation requires clinical judgment and careful study.

An important factor in the differentiation of neurogenic pain from cardiac pain is awareness of the possibility of such a condition which should be kept in mind in every case of pain in the chest, shoulders and arms. The history is usually of help since neurogenic pain rarely has the typical crushing character that many cardiac pains have. Neurologic examination may or may not show changes in the reflexes, muscular atrophy, paresthesias, etc., depending upon

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the character of the underlying disease as well as the extent of it. In the questionable cases, and therefore the most important ones from a diagnostic standpoint, obvious neurologic changes do not exist. Local tenderness in the chest wall or arm if present may be a help but often is absent. Two very important diagnostic aids are the electrocardiogram, of course, and x-ray examination of the cervical spine.

CASE I. A man age forty-six complained of severe pain in the precordium, radiating to the left shoulder and arm and of somewhat sudden onset. The pain had been paroxysmal for about forty-eight hours and his description of it was very suggestive of coronary occlusion. Physical examination was negative, blood pressure normal and electrocardiogram negative. Traction of the patient's neck relieved the pain, and pressure over the roots of the cervical plexus at the foramina intensified it. X-ray films of the cervical spine showed bony changes typical of ruptured intervertebral disc in the sixth interspace. Hemilaminectomy with removal of the extruded portion of the ruptured disc resulted in complete relief.

The foregoing case presented very few difficulties in diagnosis as the condition was quite typical. However, an occasional patient is seen in whom there exists neurogenic pain and whose electrocardiogram shows changes indicative of some degree of coronary disease. In such patients, sometimes only a long period of observation and the exercise of the best clinical judgment will determine if the patient's pain is of cardiac origin or is neurogenic, unless there are very distinctive and outstanding neurological changes.

CASE II. A sixty-four year old physician was referred for consultation. He had been kept in bed for five weeks with a diagnosis of coronary pain because of pain in the precordium radiating to the left mid-arm. The pain in his arm was of squeezing or crushing character. Bed rest had not influenced the pain although it was transiently relieved to a large extent by nitroglycerin. The electrocardiogram showed marked abnormalities with incomplete bundle branch block. After a period of observation the clinical impression was that the patient's pain was probably not cardiac in origin, and x-ray films of the cervical spine showed evidences of a ruptured intervertebral disc in the fifth interspace. Head traction was applied, and within twenty-four hours the pain had disappeared but would recur if traction were left off for too long a period. After some days of continuous traction the patient returned home symptom-free and resumed his strenuous medical practice which he has continued without interruption for four years. Occasional recurrence of the pain necessitates application of traction for a short period which results in complete relief. The electrocardiogram remains unchanged.

Another misleading situation arises when a patient has pain suggestive of coronary disease with a demonstrable basis for neurogenic pain and no objective evidence of heart disease.

CASE III. A fifty-four year old man was referred because of precordial pain radiating to the left shoulder and arm, occurring on effort, particularly that requiring use of the arms and not relieved by nitroglycerin. An electrocardiographic tracing was entirely normal as was one made while the patient had pain deliberately produced by exertion. X-ray examination of the cervical spine showed the typical changes of a ruptured disc in the fifth and sixth interspaces. After a period of study our clinical impression was that the patient's pain was coronary in origin and not neurogenic. This impression was confirmed about two weeks later by the appearance of a frank acute coronary occlusion with typical electrocardiographic and other objective signs.

II. *Pain in the Lumbar Region and Loins.* Pain in this region, we find, has been most often erroneously diagnosed as some type of urinary tract disease. We find that although the patient has had no dysuria as part of his symptoms, urinary tract disease is diagnosed on the basis of some supposed abnormality detected in pyelo-ureterograms. We find a frequent error in this respect is the diagnosis of stricture or kink of the ureter. The common practice of injecting an opaque medium into the urinary tract and making only one x-ray film results in interpreting a normal peristaltic contraction

as a stricture of the ureter, and the normal fold of the ureter on deep inspiration as a kink. This is done even in the absence of any ureterectasis above the point of supposed stricture. The simple procedure of making serial urograms, as developed by Dr. Thomas D. Moore, would eliminate this error. Another source of incorrect diagnosis is the failure to keep in mind the possibility of neurogenic pain and the fact that pain in a given area does not of necessity mean pain in a viscus; another is the failure to distinguish between superficial tenderness or hyperesthesia and the deep tenderness present in visceral disease.

CASE IV. A woman age forty-three complained of pain at times of great severity in the left lumbar region and loin. Diagnosis of strictured ureter had been made two years previously and for treatment of this, twenty-two cystoscopic procedures had been carried out over this period of time with the idea of dilating the supposed stricture. Urologic investigation, including serial pyelo-ureterograms, showed a normal urinary tract. Examination showed marked tenderness beginning in the right costovertebral angle and extending around the flank to the abdomen. The tenderness appeared to be superficial, and neurologic examination showed hyperesthesia of the skin along the area of the tenth thoracic segmental innervation on the left. Torsion of the spine reproduced the patient's pain. X-ray examination of the vertebral column was negative. Spinal fluid was entirely negative and dynamics were normal. Paravertebral injection with novocaine of the ninth, tenth and eleventh nerves on the left resulted in complete disappearance of the pain as long as the effect of the novocaine lasted. Although no evidence of an intraspinal lesion could be demonstrated, an exploratory hemilaminectomy was done and no organic lesion was found. However, as the procedure was done under local anesthesia, identification of the involved nerves was possible and a section of the posterior roots was done. Since this procedure was done three years ago, the patient has had no pain and has been perfectly well.

The foregoing case is illustrative of a group of neurogenic pains for which no organic or inflammatory basis can be demonstrated and which we must assume to be of a neuralgic type similar to the neuralgias of the cranial nerves.

CASE V. A school teacher age fifty-eight was referred by a urologist for investigation because of pain in the left lumbar region and flank of eighteen months' duration after his examination had shown no abnormality of the urinary tract. The patient had gone to him for removal of her left kidney, as a diagnosis had been made elsewhere of disease of the left kidney because of failure to visualize the kidney pelvis following intravenous injection of opaque medium. The clinical aspects of this patient were almost identical with those of the first case except the spinal fluid was xanthochromic, clotted spontaneously after withdrawal, and Queckenstedt's test showed a slight block in the spinal canal. Very little if any signs of cord compression were present, the only evidence being slight increase in activity of the left knee jerk and upon direct questioning admission by the patient of recent, slight weakness in the left leg. A laminectomy at the tenth thoracic level revealed an extramedullary meningofibroma which was removed with complete and permanent relief of pain.

III. *Abdominal Pain.* Neurogenic pain can be referred to the abdomen, leading to the diagnosis of gallbladder disease or appendicitis. An important diagnostic point in the consideration of abdominal pain is the fact that visceral disease of a degree and character sufficient to cause pain must of necessity cause some visceral dysfunction. Failure to take this point into consideration easily leads to errors in diagnosis when abdominal pain is present.

CASE VI. A woman age thirty-two consulted a surgeon because of pain very low in the right abdominal quadrant. Local tenderness was present and the surgeon made a diagnosis of "chronic appendicitis" and removed her appendix. Ten days after the operation, while the patient was still in the hospital, she complained of persistence of the same pain and the surgeon referred the patient to us as a diagnostic problem. A more detailed history showed that the abdominal pain had never been associated with any symptoms of intestinal dysfunction or nausea, but did show a relationship to pain in the right lumbosacral region radiating at

times to the right sciatic nerve. The latter pain was not considered by the patient to be of primary importance, and she did not stress it in the history given the surgeon. The history also included a severe fall in the past with pain and soreness in her back for some time. Neurologic examination showed a diminished right ankle jerk, a positive Lasègue's sign on the right and a positive Naffziger's sign. X-ray films showed narrowing of the fifth lumbar interspace, and the spinal fluid showed an increase in total protein to 80 mg. per cent; it was otherwise negative. A hemilaminectomy was done and the extruded portion of a ruptured intervertebral disc was removed with complete and lasting relief of the pain.

Situations similar to this patient's have been encountered by us many times, and the operations previously done have ranged from appendectomy to total hysterectomy.

## PATHOLOGY

The character of this discussion is obviously such that a detailed consideration of the various types of pathology in the nervous system is not appropriate. Any mechanical or inflammatory change involving sensory nerve roots can produce the clinical pictures described. In our experience the most common cause of root pains is ruptured intervertebral disc with herniation of the nucleus pulposus and associated tissue changes. Within the past few years, familiarity with ruptured discs as a cause of sciatic pain has been widespread.[1] However, it has been only recently that we have become aware of the importance of considering a ruptured disc in the cervical region as a cause of chest and arm pain simulating coronary disease; and attention was first called to this by Semmes and Murphey[2] in 1941 and again by Whiteleather, Semmes and Murphey[3] in 1944. We have found the incidence of this condition to be surprisingly high.

Next in importance are intradural extramedullary tumors of which meningeal fibroma and perineural fibroma are the most common. Of lesser incidence are sarcoma, fibroma, neurofibroma, chondroma, varices and angiomas, tuberculoma, etc.

Of the inflammatory changes, chronic arachnoiditis and pachymeningitis are probably the most important, although herpes zoster without eruption is an occasional cause of acute neurogenic pain and sometimes of chronic pain following the acute stage. The chronic ganglionitis of tabes is well known as a cause of neurogenic pain.

In the bony structure of the spine itself both benign lesions such as arthritic changes and osteomas, as well as malignant processes either primary or metastatic, can cause root pains. Tuberculous spondylitis can cause root pains months before x-ray changes in the bones appear.

Pain due to involvement of the cervical sensory roots is referred to the occipital region, the shoulder, arms and upper chest. In these areas it can simulate migraine or other types of headache, coronary pain and intrathoracic lesions.

Pain due to involvement of the upper thoracic sensory roots is often referred to an intercostal space while lower thoracic root pain is referred to the abdomen. If the pain is in the upper abdomen, it may simulate disease of the gallbladder, duodenum, stomach, colon or kidney. If referred to the lower abdomen ($T_{10}$ to $T_{12}$), the pain may be mistaken for that of disease of the appendix, and pain from involvement of the lumbar or sacral sensory roots may be referred to the bladder, rectum, inguinal region and lower abdominal quadrants. In addition to sciatic and back pain, groin or lower abdominal pain occurs in 25 per cent of ruptured discs in the lumbar region.

## DIAGNOSIS

Diagnosis of neurogenic pain is dependent to a large extent on consciousness of the possibility of such a condition when one is presented with a clinical picture of pain suggestive of visceral disease. There are certain characteristics of neurogenic pain that should be inquired into in every history in which pain is the outstanding symptom. The lesions mentioned as a cause

of root pains result in fixation of the nervous structures at the point of their location and, as a consequence of the absence of mobility, movements of the body involving bending of the spinal column very often will aggravate the pain or produce it. The same holds true with increase in intracranial pressure, and the history will often bring out the fact that the pain is aggravated by coughing, sneezing or straining at defecation. Since cutaneous paresthesias are often present along the distribution of the involved nerve, the history may show that the pressure of clothes produces discomfort.

It should not be necessary to remark on the importance of a careful general physical examination and all indicated laboratory and x-ray studies. A complete neurologic examination should be made with particular reference to certain diagnostic points. In ruptured discs in the cervical region manipulation of the neck will sometimes reproduce the pain, particularly slight tilting of the head toward the affected side and making downward pressure on top of the head. If the patient is seen while he has pain, firm traction upon the head will very often relieve the pain while traction is being applied. In the dorsal region hyperextension of the spine and forcible twisting of the spine may reproduce the patient's pain or intensify it. In the lumbar region Lasègue's test is valuable; it is carried out by flexing the thigh on the trunk with the leg extended. At any level Naffziger's test when positive is of value and consists of compressing the jugulars, preferably with a blood pressure cuff pumped up to a pressure of about 30 mm. of mercury for two minutes. A positive test reproduces or accentuates the pain. If the simple test is negative, frequently a cough will bring out the intensification or reproduction of the pain.

Spinal puncture should be done except in cases in which other evidence is unmistakably diagnostic, and Queckenstedt's test should always be performed when this is done. The total protein content of the fluid will usually be elevated when tumors or ruptured discs are present; however, a normal protein figure does not eliminate these lesions from consideration. In the chronic inflammatory lesions there often are not any distinctive spinal fluid changes except, of course, in gumma or tuberculous changes in the spine.

X-ray examinations of the spine properly done are invaluable. Anteroposterior, lateral and oblique views should be made. When a ruptured intervertebral disc has existed long enough, typical bony changes appear manifested by narrowing of the interspace, spur formation on the anterior aspects of the bodies when seen in the lateral film and frequently osteophytes projecting posteriorly. Oblique views may show narrowing of the foramina. When the typical changes have not had time to occur, an important sign in the neck is segmental straightening of the vertebral column in lateral films and even reverse curvature, either of the whole neck or of segments. In the dorsal and lumbar regions narrowing of the interspaces with the body changes mentioned are the main signs although occasionally absence of normal curvature may be present alone. In tumors the classical signs of thinning or absence of the pedicles and widening of the interpediculate distance in anteroposterior films when present are of extreme value, but when absent have no negative value.

If no distinctive x-ray changes are seen, myelography should be done, preferably using pantopaque as a contrast medium. We have never observed any bad results from this procedure when carried out by our neurosurgeons in cooperation with our roentgenologist.

The treatment is primarily neurosurgical and will not be discussed here. However, in many patients with mild degrees of pain from ruptured discs in the cervical region, relief can be obtained by sleeping on a hard bed without a pillow, or, if this is ineffective, a period of bed rest with head traction carried out by an appropriate apparatus. A most important part of treatment is assuring the patient that his pain is not due to heart disease. Many of the milder pains

due to ruptured discs in the lumbar region will be relieved by a period of rest on a firm bed.

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# Seminars on Hypertension

## Treatment of Hypertensive Vascular Disease with Rice Diet*†

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THE treatment of hypertensive vascular disease with the rice diet[1–5] was suggested by observations made on the protein, fat and carbohydrate metabolism of isolated kidney cells under various pathologic conditions (cell injury and/or changes in pH, sodium bicarbonate concentration, oxygen tension and metabolizable substrate[6–11]).

Until 1944 the consensus was that dietary treatment was useful in kidney disease but of no value in hypertensive vascular disease. "The diet in uncomplicated hypertension requires no essential change from the normal. There is no justification for restriction of protein intake, indeed, such restriction may result in anemia and other evidences of malnutrition. Likewise, in the absence of edema or paroxysmal dyspnea, the restriction of salt is unwarranted; claims that such restriction may lower the blood pressure have not been substantiated. Obesity should be avoided for the same reasons that apply to normal individuals and not because of any demonstrated relationship to hypertensive disease."[12] "No dietary treatment is known which has a specifically favorable effect on essential hypertension."[13]

The rice-fruit-sugar diet is more rigid than any of the fat-poor, salt-poor or protein-poor "hypertension" diets (the therapeutic possibilities and limitations of these will not be discussed here.) The rice diet contains in 2,000 calories not more than 5 Gm. of fat and about 20 Gm. of protein derived from rice and fruit and not more than 200 mg. of chloride and 150 mg. of sodium. A patient takes an average of 250 to 350 Gm. of rice (dry weight) daily; any kind of rice may be used provided no sodium, chloride, milk, etc. has been added during its processing. The rice is boiled or steamed in plain water or fruit juice, without salt, milk or fat. If the sodium concentration of the plain water available is greater than 20 mg. per liter, distilled water should be used. All fruit juices and fruits are allowed, with the exception of nuts, dates, avocados and any dried or canned fruit or fruit derivatives to which substances other than white sugar have been added. Not more than one banana a day should be taken. White sugar and dextrose may be used *ad libitum;* on an average a patient takes about 100 Gm. daily but, if necessary, as much as 500 Gm. daily should be used. Tomato and vegetable juices are not allowed. Usually no water is given and the fluid intake is limited to 700 to 1,000 cc. of fruit juice per day. Supplementary vitamins are added in the following amounts: vitamin A 5,000 units, vitamin D 1,000 units, thiamine chloride 5 mg., riboflavin 5 mg., niacinamide 25 mg., calcium pantothenate 2 mg. No other medication is given unless it is specifically indicated.

During the first period of "regulation" on the diet, the patient should be under constant medical supervision and blood

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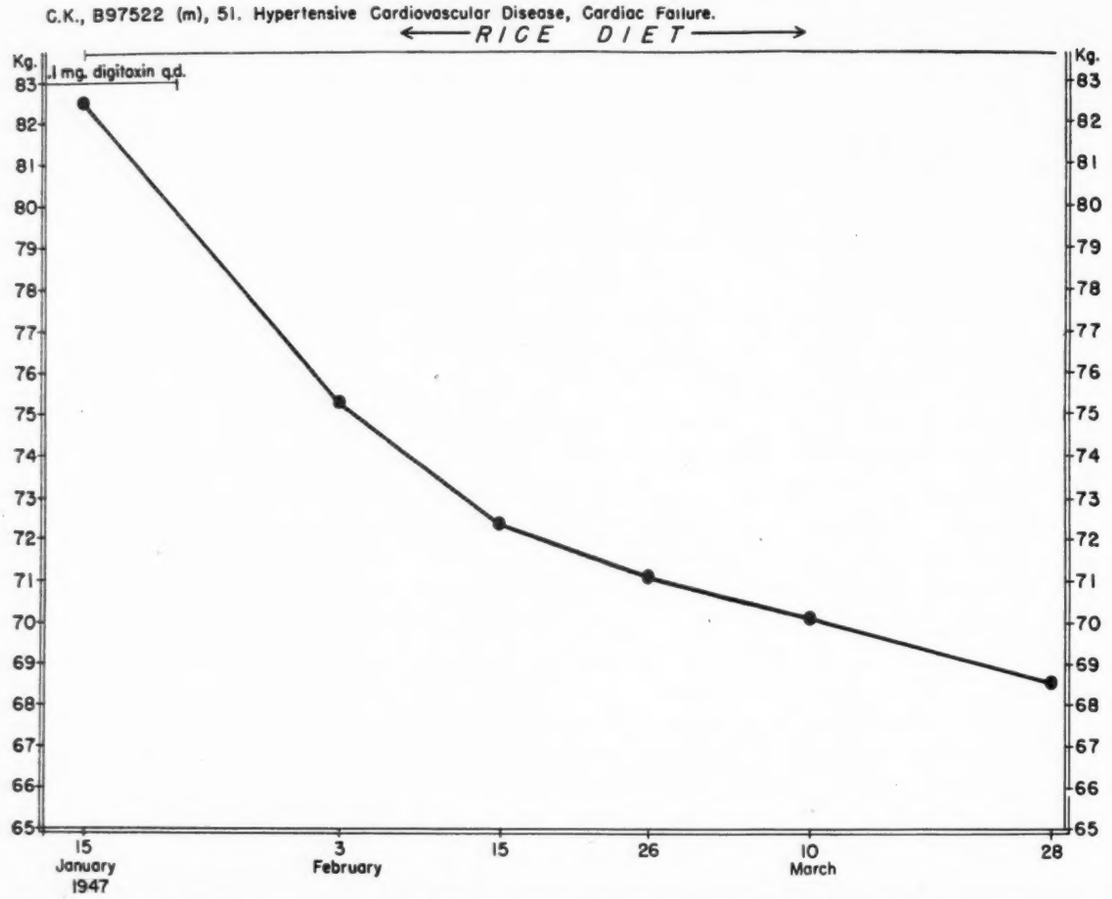



FIG. 1. C. K., male, fifty-one years of age. The patient had hypertensive vascular disease of seven years' duration, auricular fibrillation, cardiac failure of one year's duration, enlargement of liver and spleen and ascites. Previous treatment: digitalis, mercurials, ammonium chloride; codein; low salt, low fat, high protein diet; paracentesis 12 times in past year. January 15 to 21, 1947: Blood pressure, average, 174/97; NPN 44 mg. per 100 cc. blood; venous pressure 380 mm. of saline; total PSP excretion in two hours: 39 per cent. Rice diet started January 18, 1947, was strictly followed. All medication discontinued. On March 17, 1947, NPN 27 mg. per 100 cc. blood March 24 to 30, 1947: Blood pressure, average, 137/82.——Ascites and edema unchecked by digitalis, mercurials, ammonium chloride, low salt high protein diet disappeared on rice diet without medication. There was a 14 Kg. weight loss in sixty-eight days.

and urine chemistry should be checked frequently.

Rest in bed, unless the severity of the condition demands it, is neither necessary nor desirable.

It is not unusual for the weight to decrease more or less markedly during the first twenty days. The reason for this weight loss may be that the amount of food given does not cover the caloric requirements; in this case the amount of rice, fruit and sugar must be increased unless reduction of weight is indicated. Another reason may be that the patient does not eat the full amount of his diet during the first period of adjustment. The most frequent cause is the loss of visible or invisible edema; for example, one patient with marked edema lost 63 pounds in the first sixteen days on the diet (no digitalis, mercurials, etc., were given).[5] Figure 1 shows the weight chart of another patient, a fifty-one year old physician, with hypertensive heart disease and auricular fibrillation whose persistent liver enlargement, ascites and edema had not improved in spite of intensive treatment with digitalis, mercurials, ammonium chloride, salt-poor diet and frequent paracenteses.

As a rule the diet should be continued without modification until those conditions

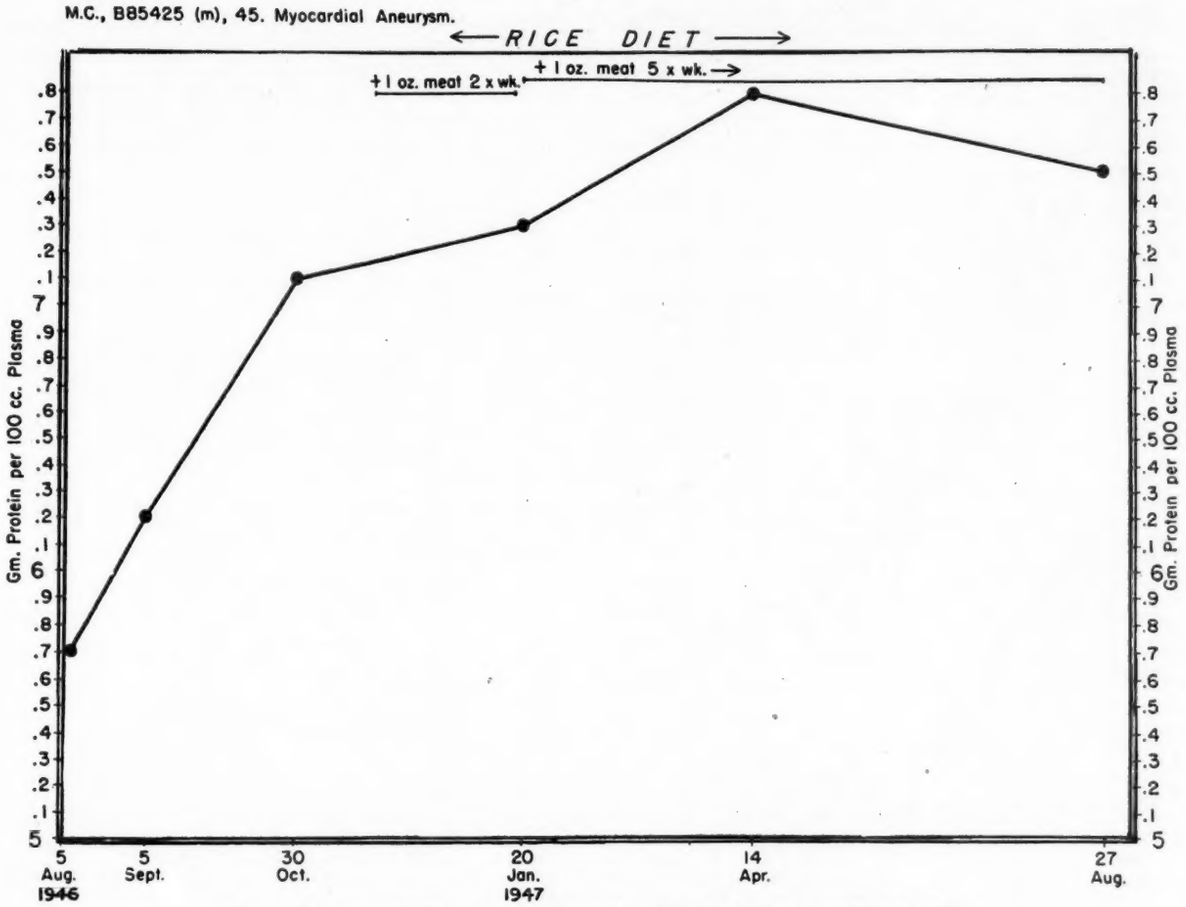



Fig. 2. Increase of plasma proteins on rice diet (for history see Figure 17).

which were the indication for its use have disappeared. Then small amounts of non-leguminous vegetables, potatoes, lean meat or fish (all prepared without salt or fat) may be added. But only so much additional food should be allowed as can be taken without producing undesirable changes in blood pressure, heart size, electrocardiogram, eyegrounds, non-protein nitrogen, etc. When a critical condition of heart, kidney or retina exists, the strict rice diet should be continued indefinitely provided that the equilibrium between intake and loss of those substances which are indispensable for the body is maintained.

## CHEMICAL CHANGES PRODUCED BY THE RICE DIET

*Nitrogen Metabolism.* Because of the protein-sparing effect of carbohydrates, the protein equilibrium is maintained in spite of the low protein content of the rice diet.

A minimum of 50 Gm. of protein (type of protein not specified) has been postulated as the so-called "wear and tear quota" necessary to cover the daily protein requirements. However, since this figure is derived from the total nitrogen excretion of fasting individuals, which is about 7 Gm. in the urine and 0.9 Gm. in the stools, it indicates only the amount of the body protein broken down in fasting ($7.9 \times 6.25 = 49.4$). In patients who have followed the rice diet for two months or more the daily urinary total nitrogen excretion is less than one third of that in fasting. It averages 2.26 Gm.[5] If an allowance of 0.9 Gm. per twenty-four hours is made for the excretion of nitrogen other than that excreted in the urine, the total nitrogen loss in twenty-four hours is about 3.16 Gm. With a daily intake

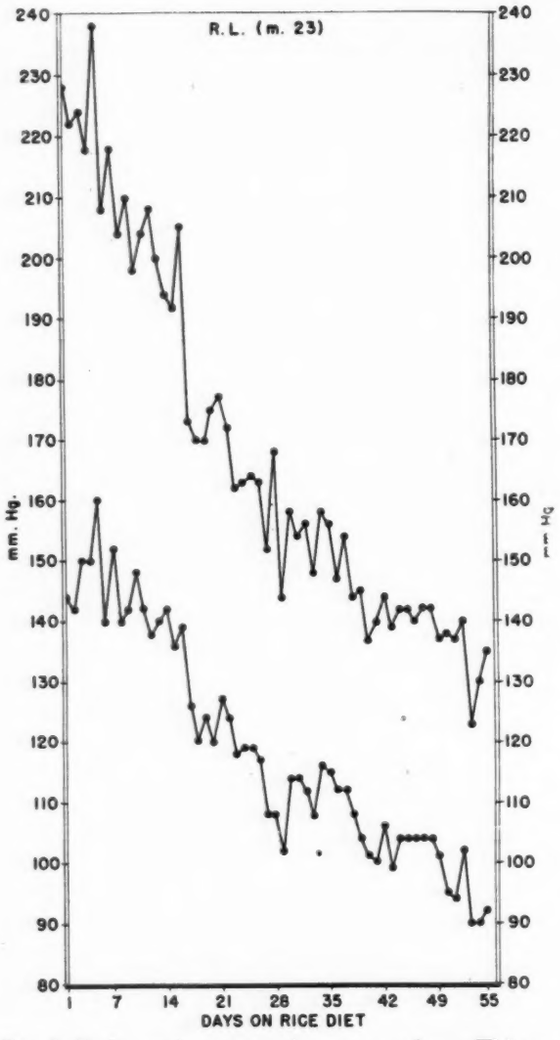



FIG. 3. R. L., male, twenty-three years of age. This patient had hypertensive vascular disease of three years' duration. He was previously treated with a "modified rice diet." EKG $T_1$ inverted. (Fig. 22.) Total PSP excretion in two hours: 2.5 per cent; NPN 79 mg. per 100 cc. blood; cholesterol 340 mg. per 100 cc. serum. There was advanced retinopathy. (Fig. 30.) Rice diet started December 18, 1945 and strictly followed for three months (8–21 mg. Cl per 100 cc. of urine). March 17, 1946: NPN 60 mg. per 100 cc. of blood; cholesterol 173 mg. per 100 cc. serum.——————Decrease in blood pressure started in first week of rice diet.

of $3.16 \times 6.25 = 19.8$ Gm. of protein, these patients are in nitrogen equilibrium.

In fasting the daily urea nitrogen excretion in the urine is about 5.5 Gm. In the urine of patients who have followed the rice diet for two months or more the average daily urea nitrogen excretion is 1.1 Gm.[5]

In fasting the blood non-protein nitrogen and the blood urea nitrogen concentrations

TABLE 1
AVERAGE NPN AND UREA-N OF 261 PATIENTS WITH HYPERTENSIVE VASCULAR DISEASE
(Initial NPN 20 to 45 mg. Per 100 cc. Blood)

| No. of Patients | Average Period of Treatment (Days) | NPN | | Urea-N | |
|---|---|---|---|---|---|
| | | Average Before Rice Diet | Average After Rice Diet | Average Before Rice Diet | Average After Rice Diet |
| | | Mg. Per 100 cc. | Mg. Per 100 cc. | Mg. Per 100 cc. | Mg. Per 100 cc. |
| NPN and Urea-N Increased | | | | | |
| 13 | 62 | 31 | 35 | 12.5 | 16.0 |
| NPN Increased, Urea-N Decreased | | | | | |
| 10 | 74 | 30 | 32 | 11.4 | 7.5 |
| NPN Decreased, Urea-N Increased | | | | | |
| 3 | 83 | 32 | 31 | 8.9 | 12.8 |
| NPN and Urea-N Decreased | | | | | |
| 235 | 109 | 34 | 26 | 14.4 | 7.3 |
| Total | | | | | |
| 261 | 106 | 34 | 27 | 14.1 | 7.8 |

are higher than normal; on the rice diet they are lower than normal.[5] Table 1 shows the non-protein nitrogen and urea nitrogen in a series of 261 non-uremic patients with hypertensive vascular disease. The non-protein nitrogen before the diet ranged from 20 to 45 mg. per 100 cc. of blood; the average was 34 mg. After the diet it ranged from 18 to 45 mg.; the average was 27 mg. The urea nitrogen before the diet ranged from 4.8 to 30.3 mg. per 100 cc. of blood; the average was 14.1 mg. After the diet it ranged from 1.2 to 30.4 mg.; the average was 7.8 mg.

In starvation, hemoglobin and plasma protein concentrations decrease; on the rice

TABLE II
EFFECT OF HIGH AND LOW PROTEIN DIETS ON URINARY TOTAL NITROGEN AND CREATININE OF NORMAL MAN (FOLIN[14])

| | 120 Gm. Protein Egg-Milk Diet (3rd Day) | 6 Gm. Protein Cream-Starch Diet (7th Day) |
|---|---|---|
| Total nitrogen (mg. N per 24 hr.) | 16,800 | 3,600 |
| Creatinine (mg. N per 24 hr.) | 580 | 600 |

TABLE III
EFFECT OF FASTING ON URINARY CREATININE AND CREATINE OF NORMAL MAN (BENEDICT[15])

| | 1st Day of Fasting (Weight 59.6 Kg.) | 6th Day (Weight 55.9 Kg.) | 12th Day (Weight 53.6 Kg.) |
|---|---|---|---|
| Creatinine (mg. N per 24 hr.) | 480 | 390 | 370 |
| Creatine (mg. N per 24 hr.) | 0 | 130 | 120 |
| Total creatine bodies (mg. N per 24 hr.) | 480 | 520 | 490 |

diet hemoglobin and plasma protein levels are maintained.[5] (Fig. 2.)

The excretion of creatinine plus creatine (total creatine bodies) has been supposed to remain fairly constant in spite of variations in protein intake and nitrogen excretion. (Table II).

The excretion of the total creatine bodies does not decrease in one to twelve days of fasting. The creatine fraction increases. (Table III.)

The excretion of total creatine bodies decreases markedly on the rice diet; the excretion of creatine does not increase. (Table IV.)

The decrease in the excretion of total creatine bodies ranged from 7 to 48 per cent, averaging 29 per cent; the decrease in weight ranged from 0 to 11 per cent, with an average of 6 per cent.

TABLE IV
CREATININE AND CREATINE IN URINE OF TWENTY-TWO PATIENTS (FIFTEEN MEN, SEVEN WOMEN) WITH HYPERTENSIVE VASCULAR DISEASE

| | Before Rice Diet | After 35 Days (av.) on Rice Diet |
|---|---|---|
| Creatinine (mg. N per 24 hr.) | 480 | 346 |
| Creatine (mg. N per 24 hr.) | 40 | 19 |
| Total creatine bodies (mg. N per 24 hr.) | 520 | 365 |

TABLE V
TOTAL SERUM CHOLESTEROL OF 284 PATIENTS WITH HYPERTENSIVE VASCULAR DISEASE

| Initial Concentration (Mg. Per 100 cc. of Serum) | | No. of Patients | Average Period of Treatment (Days) | Mg. Cholesterol Per 100 cc. of Serum (average) | | |
|---|---|---|---|---|---|---|
| | | | | Before Treatment | After Treatment | Change |
| 110–218 | Increased | 18 | 123 | 156 | 180 | +24 |
| | Increased to 220 or over | 4 | 93 | 208 | 240 | +32 |
| | Decreased or constant | 61 | 109 | 195 | 157 | −38 |
| | | 83 | 110 | 187 | 165 | −22 |
| 220–585 | Increased or constant | 10 | 146 | 250 | 262 | +12 |
| | Decreased | 59 | 76 | 320 | 253 | −67 |
| | Decreased below 220 | 132 | 81 | 273 | 177 | −96 |
| | | 201 | 82 | 286 | 204 | −82 |
| 110–585 | | 284 | 90 | 257 | 192 | −65 |

As far as the metabolism of kidney cells is concerned rice protein cannot be indiscriminately replaced by other protein. Proteins differ from each other in regard both to the type and the relative proportion of the various amino acids of which they are composed. They also differ in regard to the rate and degree of assimilation; 30 Gm. of a protein of which 88 per cent is assimilated may be preferable to 50 Gm. of a protein of which only 40 per cent is assimilated.

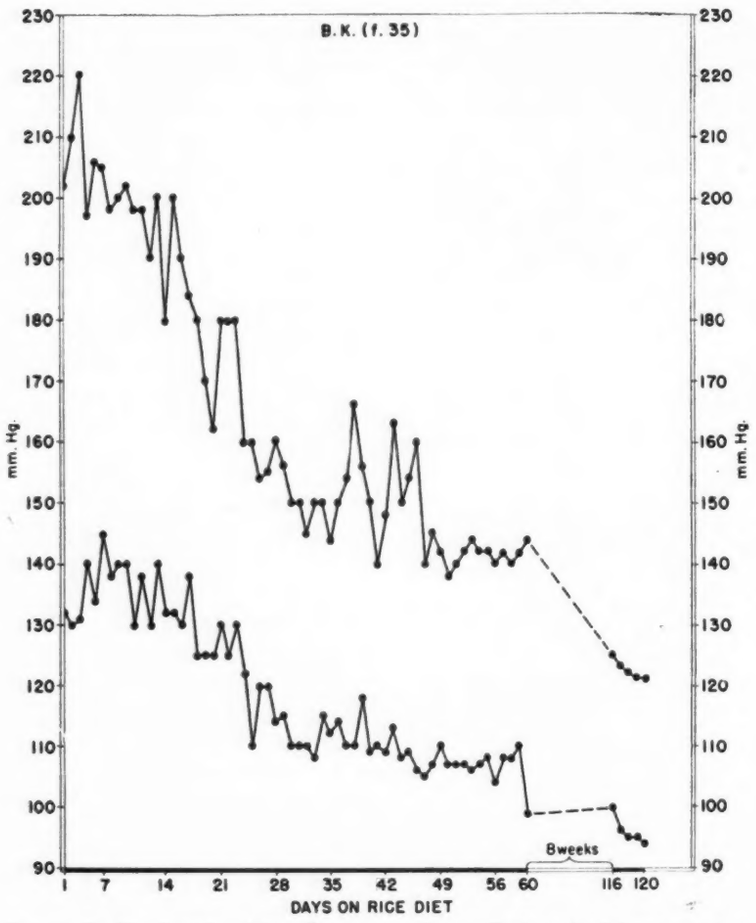



FIG. 4. B. K., female, thirty-five years of age. Patient had hypertensive vascular disease of eleven years' duration beginning during the eighth month of her second pregnancy. Of two brothers with hypertensive vascular disease, one had died at the age of thirty-seven (stroke). The patient had two retinal hemorrhages. Previous treatment: rutin, vitamin K, sedatives. Total PSP excretion in two hours 64 per cent; serum cholesterol 250 mg. per 100 cc. Rice diet was started April 23, 1947, and strictly followed (7–14 mg. Cl per 100 cc. of urine). No medication was given.———A decrease in blood pressure began in third week on rice diet.

The factor of assimilation may be important not only because of the amount of protein that can be utilized to meet the body requirements but also because of the amount of the non-utilized protein fraction, the fate and rôle of which have yet to be determined.

*Cholesterol.* The relation between serum cholesterol and vascular disease (arteriosclerosis, coronary disease, vascular retinopathy, hypertensive vascular disease) has been the subject of extensive study.

Hypercholesterolemia, regardless of its primary cause in a given case, is just as significant a metabolic disturbance as persistent hyperglycemia or hyperuricemia and should probably be considered as serious a disease, as far as potential consequences are concerned, as diabetes mellitus and gout.

Hypercholesterolemia decreases markedly with the rice diet.[1,5,11] Table v shows the effect of the diet on the total serum cholesterol concentration of 284 patients with hypertensive vascular disease. Two hundred one of these patients (i.e., 70 per cent) had hypercholesterolemia (cholesterol concen-

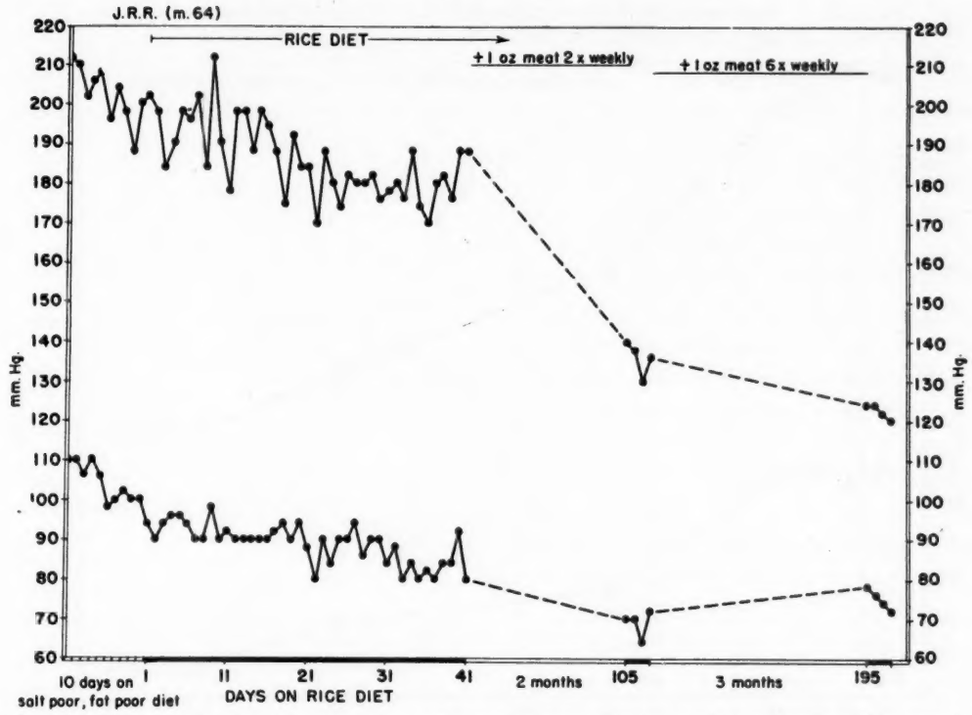



FIG. 5. J. R. R., a male, sixty-four years of age, had hypertensive vascular disease of six years' duration, four retinal hemorrhages and severe headache. He was treated previously with potassium thiocyanate. Total PSP excretion in two hours, 32 per cent. On October 7, 1946: Transverse diameter of heart, 15.2 cm; diameter of great vessels, 10.5 cm.; weight, 62.8 Kg. Rice diet was started October 17, 1946, and strictly followed (4–9 mg. Cl per 100 cc. of urine). No medication was given. The patient was working and was asymptomatic. May 2, 1947: Transverse diameter of heart, 11.9 cm.; diameter of great vessels, 8.6 cm.; weight, 64.4 Kg. No retinal hemorrhages were present. There was reduction in heart size and in size of great vessels. (Fig. 8.)——— Decrease in blood pressure was definite after 105 days.

tration of at least 220 mg. per 100 cc. serum) at the beginning of the diet.

Four patients whose serum cholesterol concentration was below the upper limits of normal had an increase to a hypercholesterolemic level (average before rice diet 208 mg. per 100 cc. serum, after rice diet 240 mg. per 100 cc. serum). One hundred thirty-two patients who had hypercholesterolemia had a decrease to a normal level (average before treatment 273, after treatment 177 mg. per 100 cc. serum). (Table v.)

Starke[16] examined the concentration of free cholesterol and cholesterol esters in the serum of seventy-nine patients with hypertensive vascular disease who had a total cholesterol concentration of 220 to 463 mg. per 100 cc. of serum at the beginning of the diet. Free cholesterol and cholesterol esters decrease on the rice diet in about the same proportion. (Table VI.)

*Chloride, Sodium, Potassium.* Therapeutic results with sodium chloride restriction such as those obtained by Allen and Sherrill[17] and by Volhard[18] were explained by Fishberg[13] on the assumption that the unpalatability of the diet led to an inadequate caloric intake and thus to a reduction of the metabolic rate. According to Page[19] the results obtained were due not to salt restriction but to "rest in bed and the psychotherapy of constant attention."

The treatment with the rice diet, which includes rigid sodium and chloride restriction, made it possible to determine the effect of a prolonged minimal intake of sodium and chloride on the concentration of these ions in blood, serum and urine.

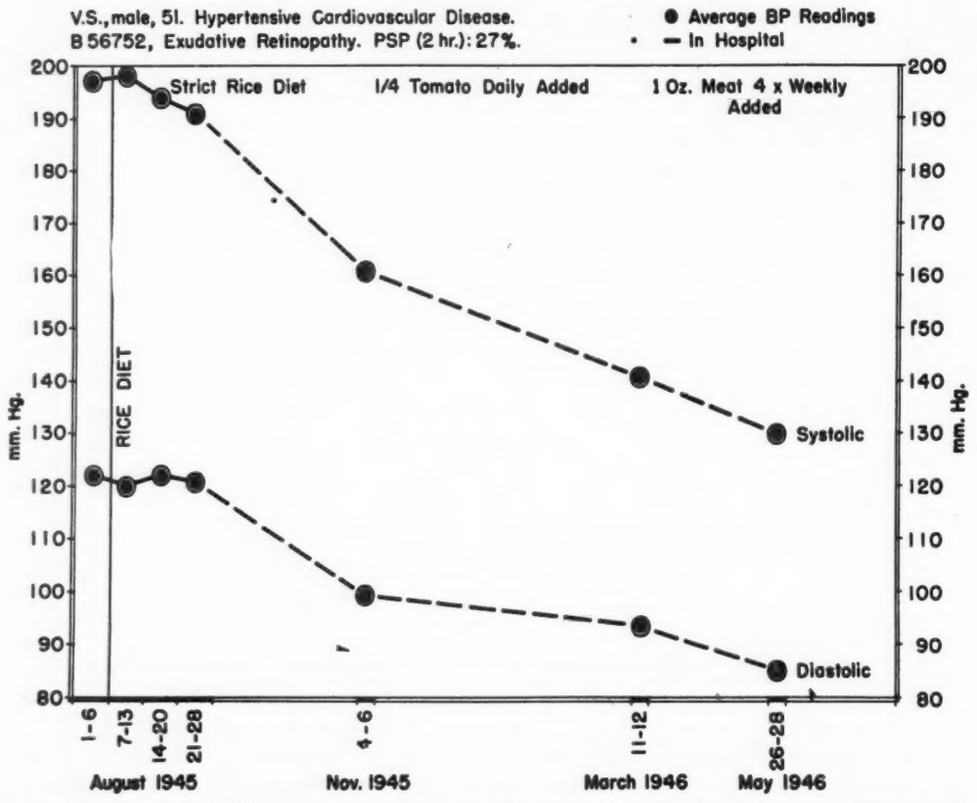



FIG. 6. V. S., a male, fifty-one years of age, had hypertensive vascular disease of eleven years' duration and retinal exudates. Previous treatment consisted of rest, sedatives and a "modified rice diet" for one month. Total PSP excretion in two hours: 21–33 per cent. Rice diet was started August 6, 1945, and strictly followed (5–20 mg. Cl per 100 cc. of urine). No medication was given. Working hours were restricted._____There was a gradual decrease of blood pressure after the third month of rice diet.

In a series of 213 patients treated with the rice diet the lowest urine chloride concentration found was 48 mg. Cl per liter with a total urinary excretion of 18 mg. Cl in twenty-four hours in a patient with hypertensive vascular disease who had been on the rice diet for seventy days. The plasma chlorides were 93.1 mEq. (as NaCl: 544 mg. per 100 cc.). The average values of 381 determinations of the plasma chlorides in ninety-one non-uremic patients with hypertensive vascular disease or primary kidney disease were: before rice diet, 97.0 mEq. per 1,000 cc. of plasma; after forty-four days (average) of rice diet, 91.7 mEq. per 1,000 cc. of plasma.[5]

Table VII gives a comparison of the concentrations of chloride, sodium and potassium in the urine of persons on a normal diet and of patients after two months on the rice diet.[11]

The average values of the chloride, sodium and potassium concentrations and their ratios in whole blood, serum and urine in thirty-seven patients with hypertensive vascular disease treated with the rice diet for an average of thirty-six days are shown in Tables VIII and IX.

In thirteen of the thirty-seven patients there was "secondary" renal involvement; in twenty-four patients there was no evidence of renal involvement. The sodium chloride content of the diet of many of these patients had been limited before they were started on the rice diet. None of these patients was in renal failure with sodium chloride leakage.

The following average changes were found: In the urine there was a decrease in the sodium concentration of 99 per cent and in the chloride concentration of 96 per cent and an increase in the potassium concentration of 78 per cent. The sodium to potassium ratio decreased by 99 per cent and the chloride to potassium ratio by 97 per cent. There was a decrease of 79 per cent in the sodium to chloride ratio. All these changes are statistically significant.

In whole blood there was a statistically significant decrease of 4.3 per cent in the sodium concentration corresponding to an increase in hemoconcentration. There was a statistically significant decrease of 5.6 per cent in the chloride concentration. The sodium to chloride ratio remained constant. There was a statistically insignificant increase of 0.8 per cent in the potassium concentration and a statistically insignificant decrease of 3.4 per cent in the sodium to potassium ratio. The chloride to potassium ratio showed a decrease of 4.7 per cent (T value 2.1; probably statistically significant).

In the serum there was a statistically insignificant decrease of 0.7 per cent in the sodium concentration. Statistically significant changes in the serum were: a decrease of 6.2 per cent in the chloride concentration; an increase of 6.1 per cent in the sodium to chloride ratio; an increase of 11.3 per cent in the potassium concentration; a decrease of 8.6 per cent in the sodium to

TABLE VI

FREE CHOLESTEROL AND CHOLESTEROL ESTERS IN THE SERUM OF 79 PATIENTS WITH HYPERTENSIVE VASCULAR DISEASE

| | Before Rice Diet | After 159 Days (Average) on Rice Diet |
|---|---|---|
| Free cholesterol (mg. per 100 cc. serum) | 80 | 61 |
| Cholesterol esters (mg. per 100 cc. serum) | 205 | 146 |
| Total cholesterol (mg. per 100 cc. serum) | 285 | 207 |

TABLE VII

URINE CHLORIDE, SODIUM, POTASSIUM ON "NORMAL" DIET AND ON RICE DIET

| | Normal Diet | Rice Diet (after 2 Months) |
|---|---|---|
| Chloride (Gm. Cl per 1,000 cc.) | 6 | 0.1 |
| Sodium (Gm. Na per 1,000 cc.) | 4 | 0.01 |
| Potassium (Gm. K per 1,000 cc.) | 2 | 3.0 |
| Gm. Na/Gm. K Ratio | 2 | 0.003 |

TABLE VIII

CHLORIDE, SODIUM AND POTASSIUM CONCENTRATIONS IN WHOLE BLOOD, SERUM AND URINE OF THIRTY-SEVEN PATIENTS WITH HYPERTENSIVE VASCULAR DISEASE BEFORE AND AFTER THIRTY-SIX DAYS (AVERAGE) ON RICE DIET

(Average Values)

| | Whole Blood | | | Serum | | | Urine | | |
|---|---|---|---|---|---|---|---|---|---|
| | Before Rice Diet | After Rice Diet | Change % | Before Rice Diet | After Rice Diet | Change % | Before Rice Diet | After Rice Diet | Change % |
| | mEq./1,000 cc. | | | mEq./1,000 cc. | | | mEq./1,000 cc. | | |
| Chloride | 80.2 | 75.7 | −5.6 | 100.8 | 94.5 | −6.2 | 86.2 | 2.50 | −96.2 |
| Sodium | 82.0 | 78.2 | −4.3 | 142.8 | 141.7 | −0.7 | 81.7 | 0.43 | −99.2 |
| Potassium | 49.5 | 49.5 | +0.8 | 4.47 | 4.86 | +11.3 | 64.4 | 88.6 | +77.8 |

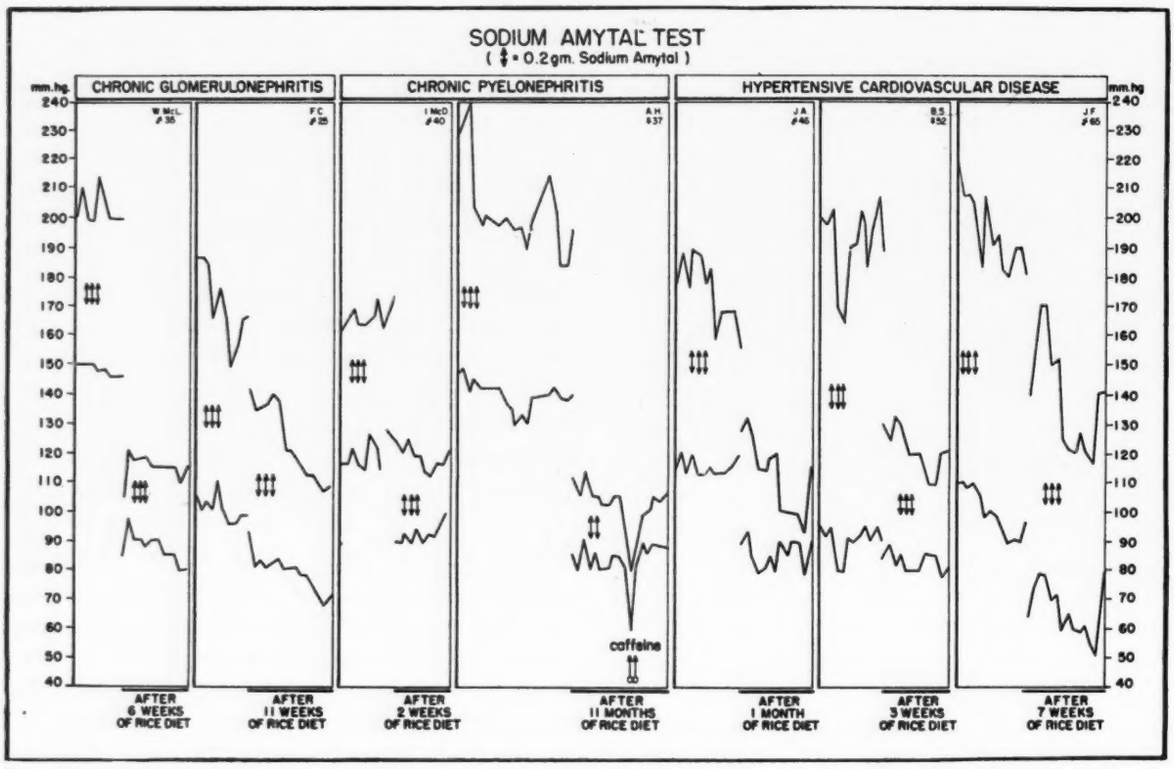



FIG. 7. Effect of 0.6 Gm. of sodium amytal on blood pressure before and after rice diet. (Reprinted from *North Carolina M. J.*, 6: 65, 1945).

TABLE IX

$\frac{\text{SODIUM}}{\text{POTASSIUM}}$, $\frac{\text{CHLORIDE}}{\text{POTASSIUM}}$ AND $\frac{\text{SODIUM}}{\text{CHLORIDE}}$ RATIOS

IN WHOLE BLOOD, SERUM AND URINE OF THIRTY-SEVEN PATIENTS WITH HYPERTENSIVE VASCULAR DISEASE BEFORE AND AFTER THIRTY-SIX DAYS (AVERAGE) ON RICE DIET

(Average Values)

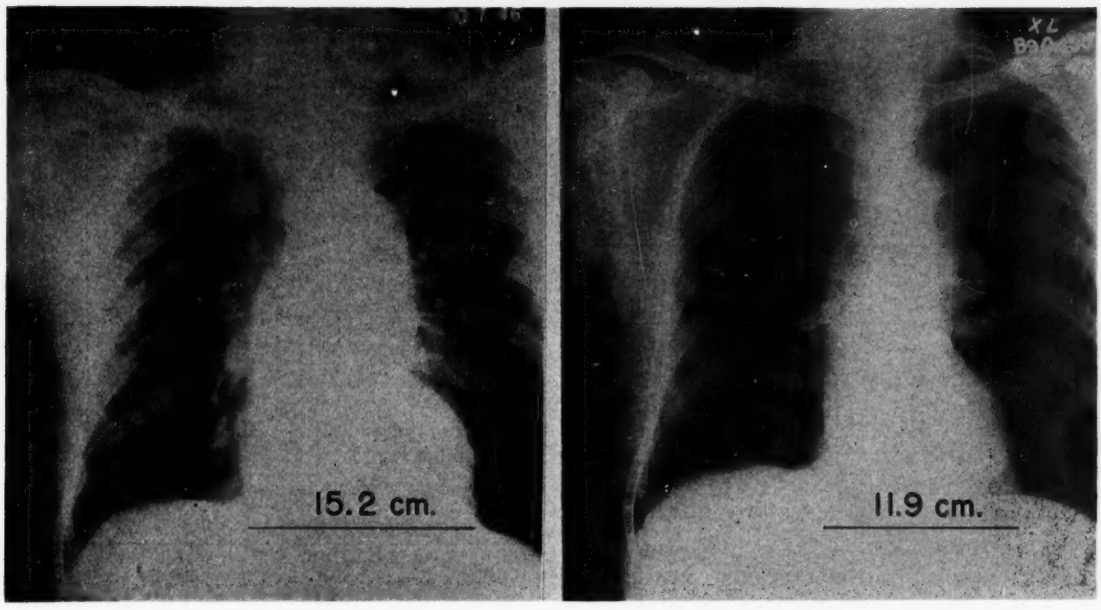
| | Whole Blood | | | Serum | | | Urine | | |
|---|---|---|---|---|---|---|---|---|---|
| | Before Rice Diet | After Rice Diet | Change % | Before Rice Diet | After Rice Diet | Change % | Before Rice Diet | After Rice Diet | Change % |
| Na/K | 1.67 | 1.61 | −3.4 | 32.7 | 29.4 | −8.6 | 1.66 | 0.006 | −99.3 |
| Cl/K | 1.63 | 1.55 | −4.7 | 23.1 | 19.6 | −14.0 | 1.71 | 0.03 | −96.9 |
| Na/Cl | 1.02 | 1.03 | +1.6 | 1.42 | 1.50 | +6.1 | 0.92 | 0.18 | −79.4 |

potassium ratio; a decrease of 14.0 per cent in the chloride to potassium ratio.

*Sulfate, Phosphate and Ammonia Excretion in Urine.* Chloride, sulfate and phosphate account for about 85 per cent of the acid excreted in the urine on a normal diet.

As Tables X and XI show the inorganic sulfate excretion in patients on the rice diet decreases by 80 per cent; the inorganic phosphate excretion decreases by 60 per cent.[20]

Ammonia is formed in the kidney by oxidative deamination of amino acids; blood and tissue acids reaching the kidney




A B

FIG. 8. J. R. R., a male, sixty-four years of age, had hypertensive vascular disease of six years' duration, four retinal hemorrhages and severe headache. He was previously treated with potassium thiocyanate (three years). A, October 7, 1946; Blood pressure 212/110; weight, 62.8 Kg.; total PSP excretion in two hours, 32 per cent. Rice diet was started October 17, 1946, and strictly followed (4–9 mg. Cl. per 100 cc. of urine). No medication was given. B, May 2, 1947; Blood pressure 122/74; weight, 64.4 Kg. No appreciable drop in blood pressure after forty-one days of diet. The patient was working. A definite drop in blood pressure was noted after 105 days of diet. (Fig. 5.) The patient was asymptomatic and retinal hemorrhages had disappeared. There was a reduction in heart size with change in transverse diameter of 28 per cent and a reduction in size of great vessels with change of 22 per cent.

TABLE X

SULFATE EXCRETION IN URINE OF FOURTEEN PATIENTS (TEN MEN, FOUR WOMEN) WITH HYPERTENSIVE VASCULAR DISEASE—NO RENAL FAILURE

| | Range | | Average | | |
|---|---|---|---|---|---|
| | Before Rice Diet | After 36 Days (Average) on Rice Diet | Before Rice Diet | After 36 Days (Average) on Rice Diet | Decrease (%) |
| | (Mg. S in 24 Hr.) | | (Mg. S in 24 Hr.) | | |
| Total sulfate | 761–471 | 254–58 | 592 | 126 | 79 |
| Inorganic sulfate | 547–362 | 165–40 | 452 | 81 | 82 |
| Ethereal sulfate | 328– 52 | 115–15 | 140 | 45 | 56 |

TABLE XI

PHOSPHATE EXCRETION IN URINE OF SEVENTEEN PATIENTS (THIRTEEN MEN, FOUR WOMEN) WITH HYPERTENSIVE VASCULAR DISEASE—NO RENAL FAILURE

| | Range | | Average | | |
|---|---|---|---|---|---|
| | Before Rice Diet | After 34 Days (Average) on Rice Diet | Before Rice Diet | After 34 Days (Average) on Rice Diet | Decrease (%) |
| | (Mg. P in 24 Hr.) | | (Mg. P in 24 Hr.) | | |
| Inorganic phosphate | 1055–501 | 435–170 | 761 | 289 | 62 |

as salts of fixed base are converted there into ammonium salts and excreted as such in the urine; thus the fixed base in the body is conserved. Under pathologic conditions (e.g., at lowered oxygen concentrations) the rate of deamination of amino acids and of ammonia production in the kidney is decreased.[6,8] The acid must be excreted in the urine as salts of fixed base, the fixed base in blood and tissues decreases and uremic acidosis follows.[9,10] In considering the significance of the figures in Tables X and XI one might speculate about the possibility of forestalling an accumulation of acids in blood and tissue fluids by restricting

TABLE XII
AMMONIA EXCRETION IN URINE OF TEN PATIENTS WITH HYPERTENSIVE VASCULAR DISEASE

| mg. $NH_3$ per twenty-four hr. | | Change (Average) |
|---|---|---|
| Before Rice Diet | After 28 Days (Average) on Rice Diet | |
| 479 | 139 | −70% |

sulfur and phosphorus in the diet, i.e., by reducing the quantity of acid formed. Or, in cases in which the kidney although functioning under pathologic conditions has retained its ability to form ammonia, one might speculate about the possibility of reducing the rate of oxygen consumption by reducing the rate of ammonia production. The amount of oxygen thus saved might lead to an increase in the oxygen concentration at the surface of kidney cells where the supply of oxygen is diminished. As Table XII shows the ammonia excretion in the urine is decreased by the rice diet.

Table XIII compares the quantities of solids excreted in the urine on the rice diet and on a normal diet.

*Discussion of the "Active Principle" of the Rice Diet.* Since the first reports on the rice diet (1944), the importance of the rigid restriction of protein, fat, sodium and chloride has been stressed. Up to that time the therapeutic effect of this diet on blood pressure, heart size, electrocardiogram, eyegrounds, non-protein nitrogen, edema, etc., had been determined in 150 patients with acute and chronic nephritis and hypertensive vascular disease.[1–4,(5)]

Grollman and Harrison (1945) believe that the effect of the rice diet is due to its low sodium content. They repeated some experiments with the rice diet on rats in which renal hypertension had been induced by the thread compression method. They confirmed our finding that the diet leads to marked blood pressure reduction. Since the hypotensive effect was not obtained when the strict rice diet was changed by the addition of NaCl (not of KCl), this

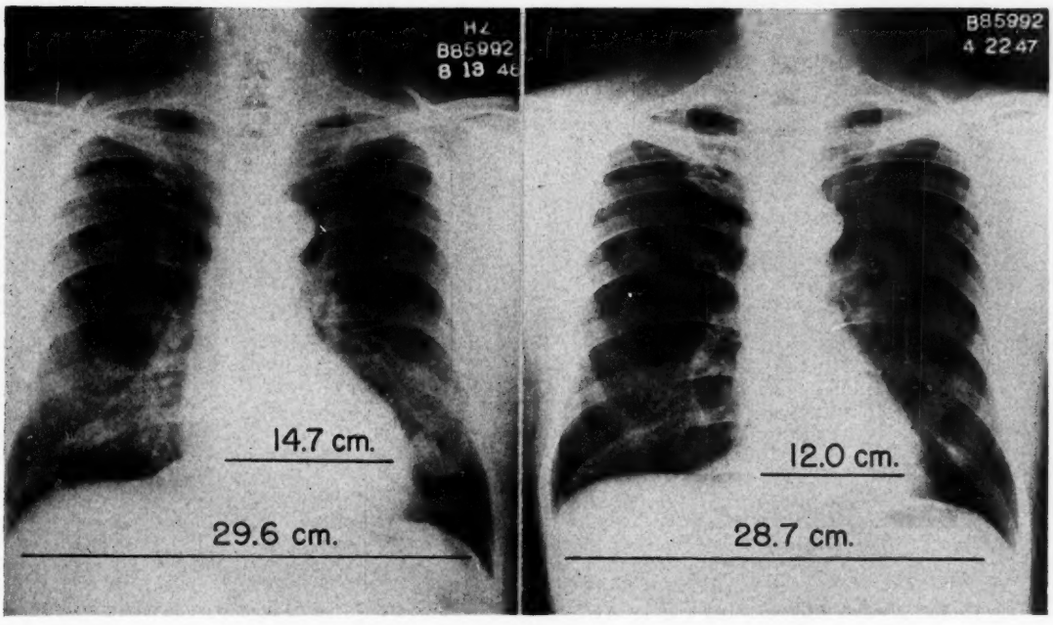
TABLE XIII
URINARY EXCRETION (GM. IN 24 HR.) ON "NORMAL" DIET AND ON RICE DIET

| | Normal Diet | Rice Diet (2 Months or More) |
|---|---|---|
| Total nitrogen | 15.0 | 2.3 |
| Urea nitrogen | 12.0 | 1.1 |
| Uric acid nitrogen | 0.3 | 0.08 |
| Total creat. nitrogen | 0.6 | 0.4 |
| Ammonia nitrogen | 0.6 | 0.1 |
| Sodium | 4.0 | 0.01 |
| Potassium | 2.0 | 3.0 |
| Chloride | 7.0 | 0.1 |
| Inorganic phosphate | 1.0 | 0.3 |
| Total sulfate | 0.80 | 0.13 |
| Inorganic sulfate | 0.72 | 0.08 |
| Ethereal sulfate | 0.08 | 0.05 |

hypotensive effect was ascribed by the authors to the sodium restriction.[21]

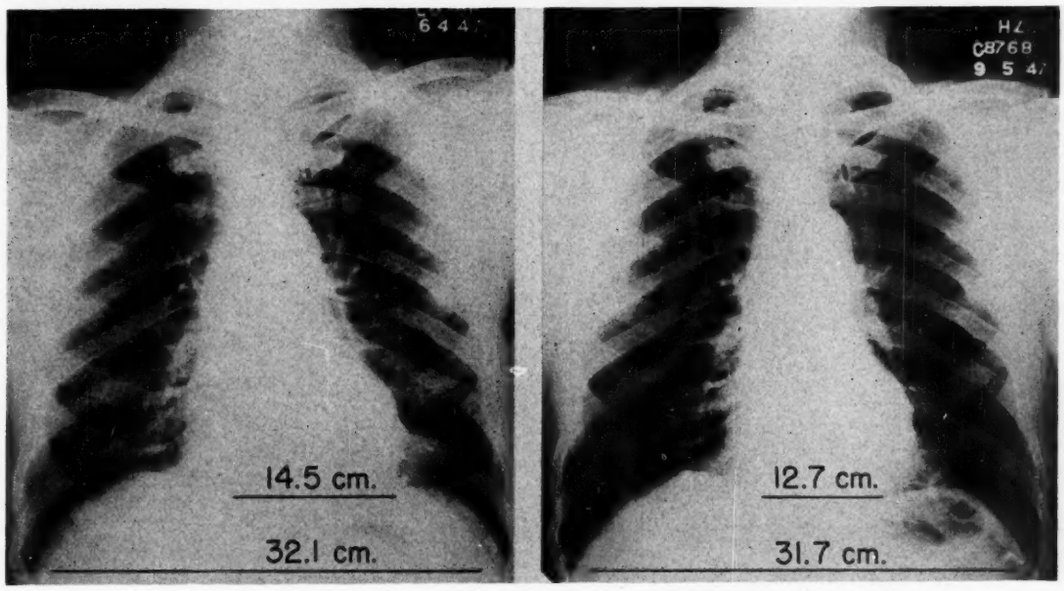
Selye and Stone (1946) kept the sodium chloride content of the diet high and varied the protein content. They produced nephrosclerosis with heart enlargement in rats by unilateral nephrectomy, lyophilized anterior pituitary gland and the substitution of a 1 per cent NaCl solution for drinking water. Each group of rats was fed exclusively on one of the following foods: skeletal muscle, cardiac muscle, "purina fox chow," peas, lentils, corn, lima beans or rice. They found that the degree of nephrosclerosis and the final organ weights were lowest in the rats fed with rice.[22]

Dock (1946) compares the relative infrequency of arteriosclerosis of the coronary arteries in the Chinese and Italian population with the high incidence of this disease in the American army and stresses the importance of cholesterol. "Diets high in cholesterol, such as the American servicemen had while in this country, may hasten the process and lead to death decades earlier than if the individual had been on a diet poor in cholesterol." "As hypertension and cholesterol metabolism become better understood and controllable there is every reason to believe that there will be a decline from the present appalling death rate from coronary disease to the insignificant level



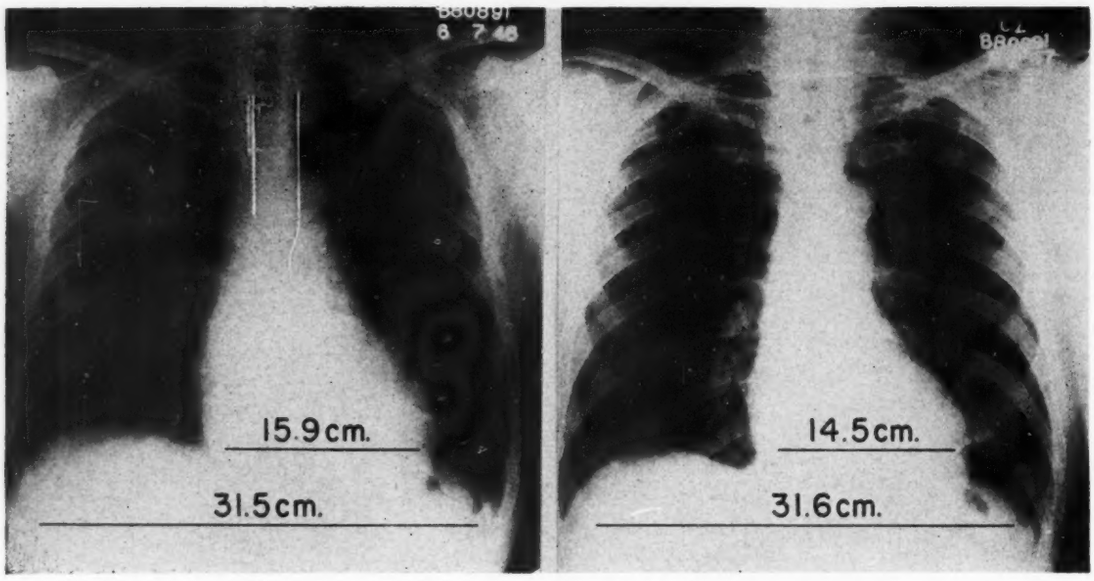

A B

FIG. 9. I. S., a male, forty-one years of age, had hypertensive vascular disease of three years' duration, retinal hemorrhages and exudates. Previous treatment consisted of rest and phenobarbital. Total PSP excretion in two hours, 60 per cent. A, August 12 to 13, 1946; Blood pressure 220/150; cholesterol 290 mg. per 100 cc. serum; EKG $T_1$ diphasic to inverted; weight, 72.5 Kg. Rice diet was started August 17, 1946 and strictly followed for two months (2–7 mg. Cl per 100 cc. of urine); then moderately well followed (35–36 mg. Cl per 100 cc. of urine). No medication was given; the patient was working. B, April 21, 1947; Blood pressure 128/88; cholesterol 155 mg. per 100 cc. of serum; EKG $T_1$ upright. Retinal hemorrhages and exudates had disappeared; weight 56 Kg._____There was decrease in blood pressure and reduction in heart size with change in transverse diameter of 22 per cent.



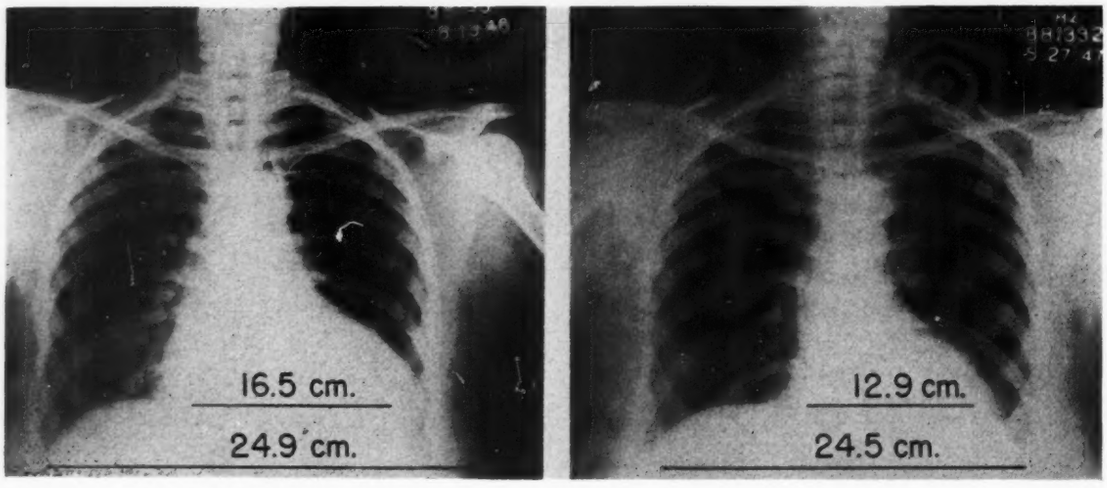

A B

FIG. 10. H. H., a male, sixty-three years of age, had hypertensive vascular disease of at least two and one-half years' duration and a stroke 1946. Previous treatment consisted of aminophyllin, rest, sedatives, weight reduction. Total PSP excretion in two hours 56 per cent. A, June 3, 1947; Blood pressure 217/124; weight, 76.3 Kg. Rice diet was started June 7, 1947, and strictly followed for three months (9-23 mg. Cl per 100 cc. of urine.) No medication was given. B, September 7, 1947; Blood pressure 170/98; weight, 70.7 Kg. _____There was a decrease in blood pressure and a reduction in heart size with change in transverse diameter of 14 per cent.



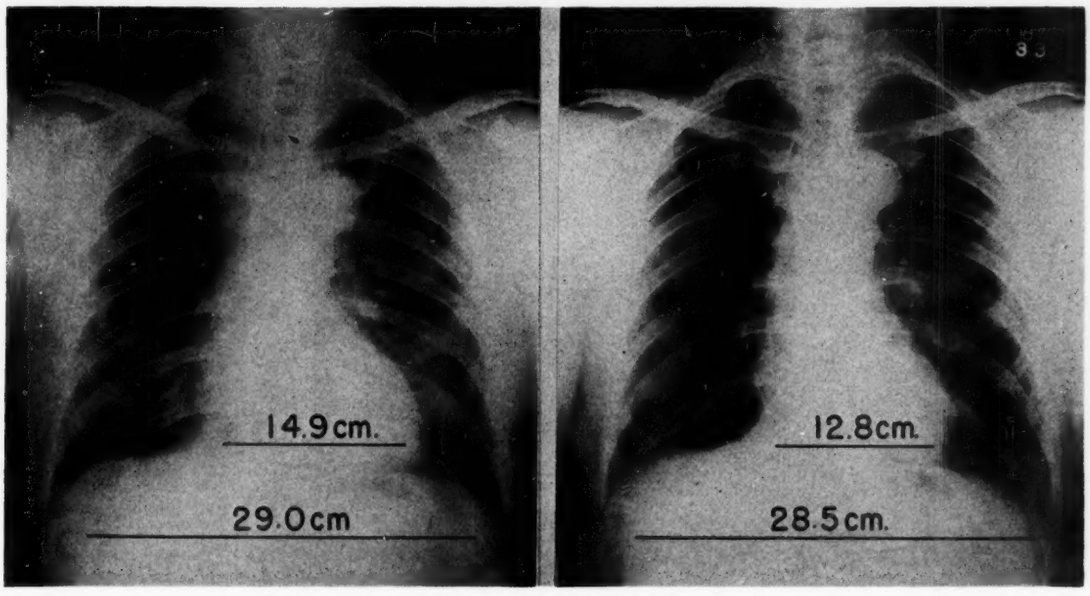

A B

FIG. 11. R. H., a male, fifty-two years of age, had hypertensive vascular disease of three years' duration and pulmonary edema. Was treated with digitalis, mercuhydrin, aminophyllin and morphine. Total PSP excretion in two hours 39 per cent. A, June 8, 1946; Blood pressure 222/130; weight, 78.7 Kg. Rice diet was started June 12, 1946, and strictly followed for four months (11–22 mg. Cl per 100 cc. of urine); then moderately well followed (43–48 mg. Cl per 100 cc. of urine). All medication except digitalis was discontinued at beginning of rice diet. Digitalis was discontinued 7–24–46. B, May 31, 1947; Blood pressure 178/106; weight 71.2 Kg.; the patient was asymptomatic and resumed his practice as surgeon.———There was a decrease in blood pressure and reduction in heart size with change in transverse diameter of 10 per cent.



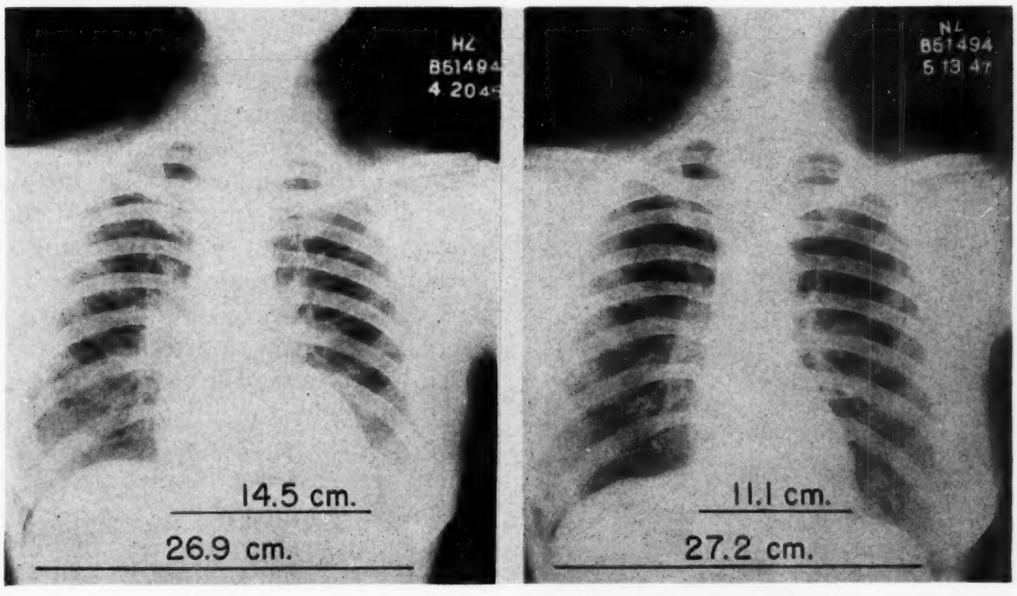

A B

FIG. 12. A and B. G. H., a female, forty-five years of age, had hypertensive vascular disease of at least three years' duration, retinal hemorrhages and exudates. Total PSP excretion in two hours, 52 per cent. A, June 14, 1946; Blood pressure 258/138; EKG $T_1$ inverted; weight, 64.8 Kg. Rice diet was started June 20, 1946, and strictly followed for four months (4–13 mg. Cl per 100 cc. of urine); then moderately well followed (26–31 mg. Cl per 100 cc. of urine); no medication was given. The patient was active. B, May 28, 1947; Blood pressure 184/98; EKG $T_1$ upright; weight 59.6 Kg. No retinal hemorrhages or exudates were present.———There was a decrease in blood pressure and reduction in heart size with change in transverse diameter of 28 per cent.



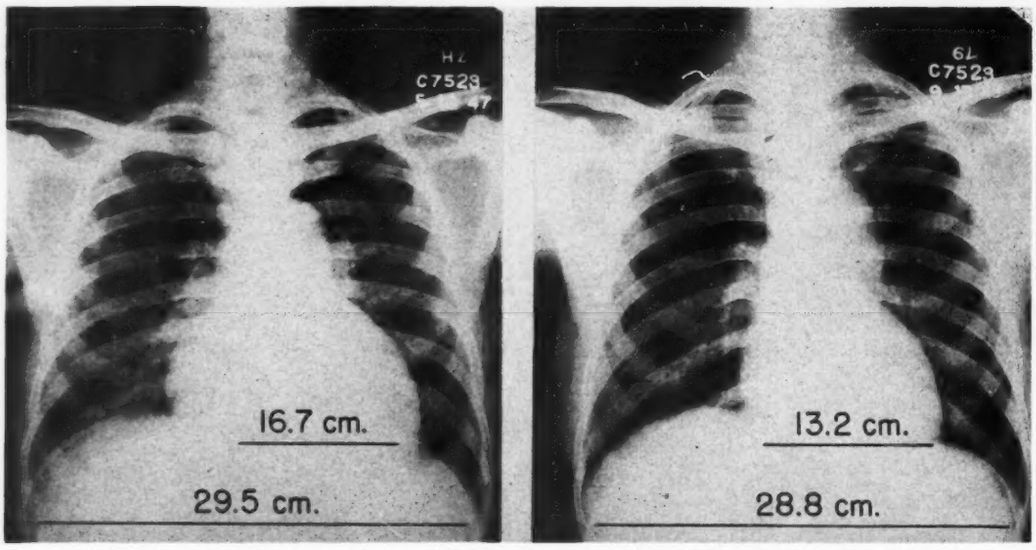

A B

FIG. 13. A and B. O. P., a male, forty-one years of age, had hypertensive vascular disease of five years' duration with severe headache. September 5, 1946; Blood pressure 186/122; EKG $T_1$ inverted; total PSP excretion in two hours 79 per cent; weight 68.7 Kg. Rice diet was started September 9, 1946; no medication was given. He was asymptomatic and able to do his work. On April 1, 1947; Blood pressure 150/100; EKG $T_1$ upright; weight, 66.4 Kg.———There was a decrease in blood pressure and reduction in heart size with change in transverse diameter of 16 per cent.




A B

FIG. 14. A and B, R. Z., a female, fifty-three years of age, had hypertensive vascular disease (of at least five years' duration) and diabetes mellitus. Previous treatment: reduction diet (25 pound weight loss). April 19, 1945; Blood pressure 202/140; weight 53 Kg.; BMR ×45 per cent; total PSP excretion in two hours 62 per cent, sugar, 231 mg. per 100 cc. blood (no insulin). Rice diet was started April 22, 1945; it was well followed through May, 1945, and from January, 1946 to February, 1947 (7–15 mg. Cl per 100 cc. of urine). No digitalis was given. From August, 1945 to December, 1946, 10–30 units of insulin were given daily. May 13, 1947: sugar, 113 mg. per 100 cc. blood (no insulin). May 14, 1947; Blood pressure 224/112; weight, 50 Kg.; BMR −10 per cent.———There was reduction in heart size with change in transverse diameter of 31 per cent in spite of persistence of high blood pressure.




A B

FIG. 15. A and B, J. P., a male, forty-two years of age, had hypertensive vascular disease of ten years' duration and cardiac failure of six months' duration. Previous treatment: sympathectomy in 1940 and from 1940 to 1946 potassium thiocyanate and phenobarbital. In 1946 pituitary irradiation was given; since 1946, digitalis, mercurials and sedatives (0.6 Gm. sodium amytal daily). May, 1947: Total PSP excretion in two hours, 32 per cent; venous pressure 195 mm. of saline. May 17 to 27, 1947; Blood pressure 220/152; weight 60.3 Kg. Rice diet was started on May 17th and strictly followed for four months. All medication was discontinued on May 17th except digitalis which was discontinued June 9, 1947. September 8, 1947; Blood pressure 214/148; weight 57.1 Kg._____A reduction in heart size occurred with change in transverse diameter of 27 per cent, in spite of persistence of high blood pressure.

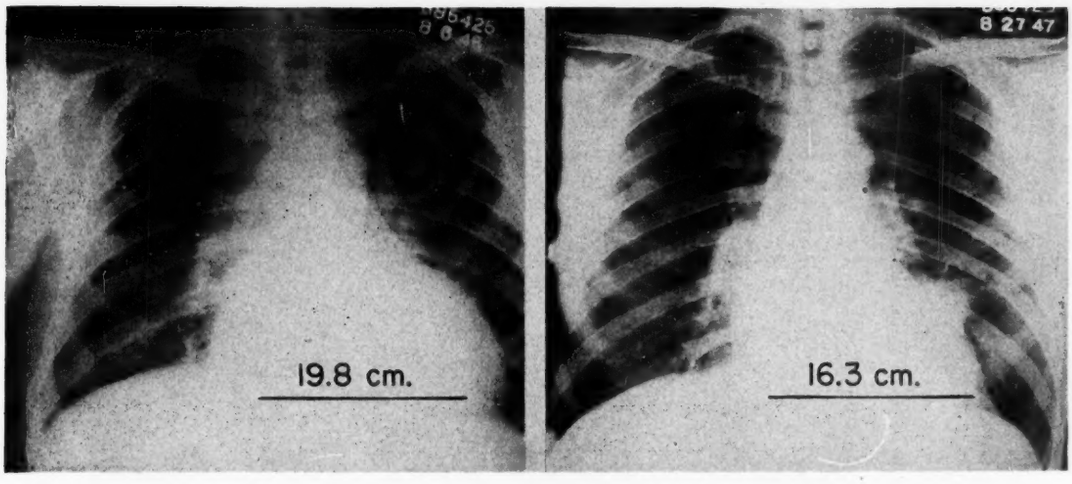
FIG. 16. M. C., a male, forty-five. Planogram of myocardial aneurysm. (See Figure 17.)

now prevailing in other populations such as the Chinese."[23,24]

G. Dick and Schwartz (1947) measured the arterial pressure in dogs in which hypertension had been produced by a nephrosclerosis which followed the intravenous administration of streptococci. At the time when the rice diet was started the hypertension had been maintained for two to four years. Dick and Schwartz found an average decrease of the mean arterial pressure from 181.6 to 138 mm. Hg after eight weeks on the diet. They conclude: "It appears that the Kempner regime is capable of causing significant lowering of the arterial blood pressure of dogs made hypertensive through the induction of nephrosclerosis. The role of weight loss, salt restriction, and nitrogen balance in this result requires further study."[25]

### INDICATIONS AND CONTRAINDICATIONS

The apparent simplicity of the rice diet has not infrequently proved a handicap.




A B

FIG. 17. A and B, M. C., a male, forty-five years of age, had a history of hypertension in 1944, myocardial infarction in 1945, followed by myocardial aneurysm.[26] There was progressive cardiac failure with massive peripheral edema, ascites, liver enlargement, hypoproteinemia (Fig. 2), hypocalcemia, albuminuria, decubitus ulcer and dyspnea. Previous treatment: (four months' hospitalization) low-protein, salt-poor diet, oxygen, digitalis, salyrgan, aminophyllin, ammonium chloride, theominal, coramine, sedatives; i.v. glucose; paracentesis. Rice diet was started August 7, 1946, and strictly followed; paracentesis August 13th; oxygen inhalation. No medication was given except digitalis which was discontinued October 10, 1946. Blood pressure August 6, 1946 was 138/94, August 27, 1947, 118/94. Advanced myocardial failure unchecked by previous intensive treatment was compensated by rice diet. The patient became asymptomatic and reduction in heart size occurred with change in transverse diameter of 21 per cent.

We have seen patients who had been treated with the diet just because the manometer had shown blood pressure figures above normal and in whom tumors, infections, etc. had been overlooked.

The rice diet is indicated in all serious instances of acute and chronic nephritis;[1–5,11] in heart failure which does not respond to the customary treatment with salt restriction and drugs;[1–5,11,26] in arteriosclerotic and hypertensive vascular disease with cardiac, cerebral, retinal or renal involvement.[1–5,11,26]

The rice diet should be tried in uncomplicated hypertensive vascular disease when a more liberal regimen (fat-poor, salt-poor diets, weight adjustment, restriction of activities, regulation of bowel habits, sedation, etc.) has failed.

The rice diet should be used as a therapeutic test before sympathectomy is considered. If the dietary treatment proves ineffective, it can be discontinued.

In cases complicated by peptic ulcer the rice diet has to be modified. The rice is well tolerated, but raw fruit should be avoided and only cooked, strained fruit should be used. Water or dialyzed milk may be substituted for the fruit juices.

The rice diet is not contraindicated in cases complicated by diabetes mellitus. It may in fact have a special value because of the dangerous rôle played by hypercholesterolemia in this disease.[27] It was expected that in order to maintain the previous blood sugar levels larger amounts of insulin would have to be given. We found instead that in many cases the blood sugar decreased on the rice diet and the insulin dose had to be reduced.

The rice diet is contraindicated unless frequent checks of the patient's blood and urine chemistry are possible. This is of especial importance in patients with renal sodium chloride leakage as the following history may illustrate:

A patient with hypertensive heart disease (Figs. 18 and 19) had been on the diet for seven months. He had followed it very strictly. After three weeks on the diet the serum chloride was 95 and the serum

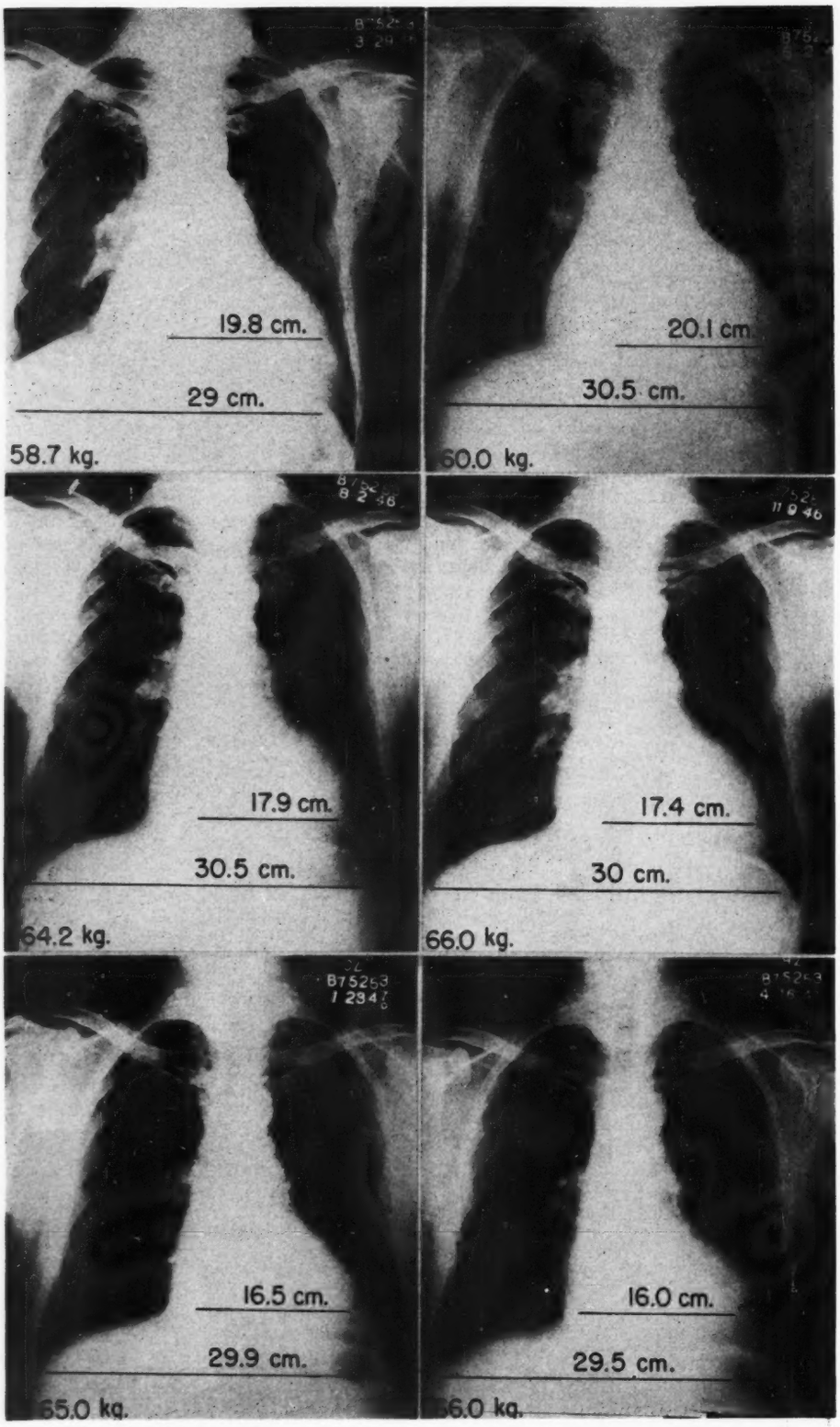



FIG. 18. P. K., a male, fifty-six years of age, had a history of nephrolithiasis, hypertensive vascular disease of more than ten years' duration, nephrectomy (left) in 1940, heart disease of three years' duration; left bundle branch block; dyspnea, edema. Previous treatment: salt-poor diet, digitalis, squill, salyrgan, mercupurin, ammonium chloride, sedatives. Total PSP excretion in two hours, 24 per cent; NPN 45 mg. per 100 cc. of blood; blood pressure 145/90. Rice diet was started April 3, 1946, and strictly followed (1–10 mg. Cl per 100 cc.of urine). All medication discontinued except digitalis. Digitalis was discontinued April 20, 1946._____There was a weight gain of 7.3 Kg and a gradual decrease in heart size.

sodium 135 mEq. per liter; after four months, 87 and 138 mEq. respectively. From the fifth month on he had felt well and had been completely asymptomatic. One evening, after some hours work at carpentry, he suddenly became unconscious and remained so for many hours. His hands and feet were extremely cold and, on regaining consciousness, he felt very weak and "faint." The attending internist who was familiar with the treatment made a diagnosis of stroke. However, on the addition of a few vegetables to his diet, all the symptoms disappeared and three days later when the patient was brought to our hospital, examination of the serum revealed a chloride concentration of 69 and a sodium concentration of 125 mEq. per liter.

### CLINICAL CHANGES PRODUCED BY THE RICE DIET

A great many patients on the rice diet have experienced relief from headache, giddiness, fatigue, dyspnea and substernal pain. Such subjective improvement has not been accepted as evidence of successful therapy. Only measured results such as decrease in blood pressure, reduction in heart size, loss of edema and reversion of electrocardiogram or eyeground changes have been used to determine the effect of the treatment.

The therapeutic results in eighty patients with acute or chronic primary kidney disease and in 130 patients with hypertensive vascular disease were reported in 1945.[5] By 1946 one hundred patients with primary kidney disease and 222 patients with hypertensive vascular disease had been treated with the rice diet.[11] This paper is limited to the changes obtained in patients with hypertensive vascular disease.

The effect of the diet has been determined in 500 patients most of whom were seriously ill and had failed to respond to other forms of treatment. The diet has been ineffective in 178 of these 500 patients if we include twenty-six patients who were in a critical condition when started on the diet and who died after an average period of thirty-nine days. In 322 of the 500 patients the diet has proved beneficial, i.e., it has produced one or more of the following effects: decrease in "mean" arterial blood pressure of at least 20 mm. Hg; reduction in heart size with change in the transverse diameter of 18 per cent or more; a change in $T_1$ from completely inverted to upright; disappearance of severe retinopathy.

*Blood Pressure.* Five hundred patients (207 women, 293 men) with hypertensive vascular disease whose "mean" arterial pressure (sum of systolic and diastolic pressures divided by 2) was 125 mm. Hg or more were treated with the rice diet. The age ranged from nineteen to seventy-three (average, fifty-one) years. Two hundred twenty-nine patients had signs of renal involvement; in 271 no conclusive evidence of renal involvement was found.

The systolic blood pressure levels before treatment ranged from 154 to 264 mm. Hg; the average was 199 mm. The diastolic blood pressure levels ranged from 72 to 172 mm. Hg; the average was 117 mm. Hg.

After they were regulated on the diet under our supervision, most of the patients followed the diet at home, returning at intervals of two to six months for reexamination.

The blood pressure was considered improved if the "mean" arterial pressure had decreased by at least 20 mm. Hg.

The results are summarized in Table XIV. The figures given are averages of the daily readings of three to twenty-four (average, eight) days before and after treatment.

Of the 229 patients in whom the diagnosis of hypertensive vascular disease with "secondary" renal involvement was made, twenty-five died six to ninety-six days (average, thirty-nine days) after the diet was started. Of the 271 patients without evidence of renal involvement, one patient died thirty-six days after the rice diet was started.

Table XV shows the difference in the percentage of improvement when these twenty-six patients who died are not included.

TABLE XIV

EFFECT OF RICE DIET ON BLOOD PRESSURE OF 500 PATIENTS WITH HYPERTENSIVE VASCULAR DISEASE (PERIOD OF DIET 4–898 DAYS) AVERAGES

| No. of Patients | Blood Pressure: Before Rice Diet | Blood Pressure: After Rice Diet | Change in Systolic and Diastolic Pressure | Change in "Mean" Arterial Pressure | Days on Rice Diet |
|---|---|---|---|---|---|
| **With Renal Involvement** | | | | | |
| *Hypertension Not Improved* | | | | | |
| 74 | 206/121 | 191/117 | −15/−4 | −9.5 | 71 |
| 25 | 226/147 | Died | ..... | ..... | 39 |
| *Hypertension Improved* | | | | | |
| 130 | 207/121 | 159/98 | −48/−23 | −35.5 | 81 |
| **Without Evidence of Renal Involvement** | | | | | |
| *Hypertension Not Improved* | | | | | |
| 89 | 186/109 | 167/102 | −19/−7 | −13 | 68 |
| 1 | 248/138 | Died | ..... | .... | 36 |
| *Hypertension Improved* | | | | | |
| 181 | 193/113 | 147/93 | −46/−20 | −33 | 85 |
| **Total** | | | | | |
| *Hypertension Not Improved* | | | | | |
| 163 | 195/114 | 178/109 | −17/−5 | −11 | 69 |
| 26 | 227/147 | Died | ..... | .... | 39 |
| *Hypertension Improved* | | | | | |
| 311 | 199/116 | 152/95 | −47/−21 | −34 | 83 |

TABLE XV

PERCENTAGE OF POSITIVE AND NEGATIVE BLOOD PRESSURE RESULTS (A) INCLUDING AND (B) NOT INCLUDING TWENTY-SIX PATIENTS WHO DIED

| A | | B | |
|---|---|---|---|
| 229 Patients with Renal Involvement | % | 204 Patients with Renal Involvement | % |
| Not improved | 44 | Not improved | 37 |
| Improved | 56 | Improved | 63 |
| 271 Patients without Evidence of Renal Involvement | % | 270 Patients without Evidence of Renal Involvement | % |
| Not improved | 33 | Not improved | 33 |
| Improved | 67 | Improved | 67 |
| All 500 Patients | % | All 474 Patients | % |
| Not improved | 38 | Not improved | 35 |
| Improved | 62 | Improved | 65 |

TABLE XVI

INFLUENCE OF THE LENGTH OF TREATMENT WITH THE RICE DIET: BLOOD PRESSURE CHANGES IN PATIENTS WITH HYPERTENSIVE VASCULAR DISEASE

| | Period of Treatment: 4–34 Days | Period of Treatment: 35–898 Days |
|---|---|---|
| | With Renal Involvement | With Renal Involvement |
| Number of patients | 86 | 143 |
| Not improved | 49 = 57%* | 50 = 35%† |
| Improved | 37 = 43% | 93 = 65% |
| | Without Evidence of Renal Involvement | Without Evidence of Renal Involvement |
| Number of patients | 109 | 162 |
| Not improved | 47 = 43% | 43 = 27%‡ |
| Improved | 62 = 57% | 119 = 73% |
| | Total | Total |
| Number of patients | 195 | 305 |
| Not improved | 96 = 49% | 93 = 30% |
| Improved | 99 = 51% | 212 = 70% |

* Including 13 patients who died.
† Including 12 patients who died.
‡ Including 1 patient who died.

TABLE XVII

CHANGES IN DIASTOLIC PRESSURE OF 406 PATIENTS WITH HYPERTENSIVE VASCULAR DISEASE INITIAL DIASTOLIC PRESSURE OF 100–159 MM. HG.

| | No. of Patients | Percentage | Average Change |
|---|---|---|---|
| Decrease of 30 mm. Hg or more | 52 | 13 | −36 |
| Decrease of 20–29 mm. Hg | 101 | 25 | −24 |
| Decrease of 10–19 mm. Hg | 158 | 39 | −14 |
| Decrease of 0–9 mm. Hg | 77 | 19 | − 5 |
| Increase of 1–22 mm. Hg | 18 | 4 | + 7 |
| Total | 406 | 100 | −16.7 |

Figures 3 to 6 show typical blood pressure curves of patients on the rice diet.

The length of time required for the blood pressure to decrease varies from four days to ten months. The part played by the

TABLE XVIII

EFFECT OF RICE DIET ON HEART SIZE: AVERAGE CHANGES IN TRANSVERSE DIAMETER OF HEART IN 286 PATIENTS WITH HYPERTENSIVE VASCULAR DISEASE

| | No. of Patients | Percentage | Period of Rice Diet (Average) Days | Diameter of Chest (Averages) | | | | Transverse Diameter of Heart (Averages) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Before Rice Diet Cm. | After Rice Diet Cm. | Change Cm. | Change % (Diameter of Chest of Smaller Heart = 100%) | Before Rice Diet Cm. | After Rice Diet Cm. | Change Cm. | Change % (Transverse Diameter of Smaller Heart = 100%) |
| Decrease of 20% or more | 19 | 6.7 | 187 | 29.5 | 28.9 | −0.6 | −2.2 | 15.3 | 12.3 | −3.0 | −24.4 |
| Decrease of 10.0–19.9% | 106 | 37.1 | 114 | 29.2 | 29.1 | −0.1 | −0.3 | 14.5 | 12.7 | −1.8 | −14.2 |
| Decrease of 0–9.9% | 146 | 51.0 | 112 | 28.6 | 28.4 | −0.2 | −0.7 | 13.8 | 13.0 | −0.8 | −6.2 |
| Increase of 0–8.0% | 15 | 5.2 | 184 | 27.5 | 27.8 | +0.3 | +0.8 | 13.1 | 13.5 | +0.4 | +2.6 |
| Total | 286 | 100 | 122 | 28.8 | 28.6 | −0.2 | −0.7 | 14.2 | 12.9 | −1.3 | −10.1 |

TABLE XIX

CHANGES IN THE ANGLE OF THE ELECTRICAL AXIS IN 292 PATIENTS WITH HYPERTENSIVE VASCULAR DISEASE AFTER RICE DIET

| No. of Patients | Percentage | Angle of Electrical Axis (Degrees) | | | | Period on Rice Diet (Av.) Months |
|---|---|---|---|---|---|---|
| | | Range of Change | Before Rice Diet | After Rice Diet | Change (Average) | |
| 1 | 2 | More than −25 | −10 | −55 | −45 | 2 |
| 6 | | −15 to −25 | +19 | 0 | −19 | 4 |
| 173 | 60 | ±14 | +13 | +17 | + 4 | 6 |
| 70 | 38 | +15 to +25 | +13 | +32 | +19 | 7 |
| 42 | | More than +25 | + 6 | +43 | +37 | 8 |

TABLE XX

CHANGES OF $T_1$ IN 310 PATIENTS WITH HYPERTENSIVE VASCULAR DISEASE AFTER RICE DIET

| No. of Patients | $T_1$ Before Rice Diet | $T_1$ After Rice Diet | Period on Rice Diet (Average) Months |
|---|---|---|---|
| | Change in Direction to Inverted | | |
| 2 | diphasic | inverted | 3 |
| 1 | upright | diphasic | 6 |
| 3 | low upright | diphasic | 4 |
| 1 | upright | low upright | 2 |
| | No Change | | |
| 52 | inverted | inverted | 5 |
| 21 | diphasic | diphasic | 4 |
| 5 | low upright | low upright | 2 |
| 136 | upright | upright | 6 |
| | Change in Direction to Upright | | |
| 19 | low upright | upright | 5 |
| 4 | diphasic | low upright | 7 |
| 19 | diphasic | upright | 8 |
| 17 | inverted | diphasic | 7 |
| 5 | inverted | low upright | 7 |
| 25 | inverted | upright | 10 |

length of time the diet was followed is evident from Figures 3 to 6 and Table XVI.

In 125 of the 500 patients (forty with and eighty-five without evidence of renal involvement) the blood pressure figures returned to normal or almost normal values (below 145/95 mm.). The blood pressure of these patients before the rice diet ranged from 222/148 to 158/98, average 181/107 mm.; the average pressure after four to 898 days, average ninety-four days, of rice diet was 132/85 mm. Seven patients are

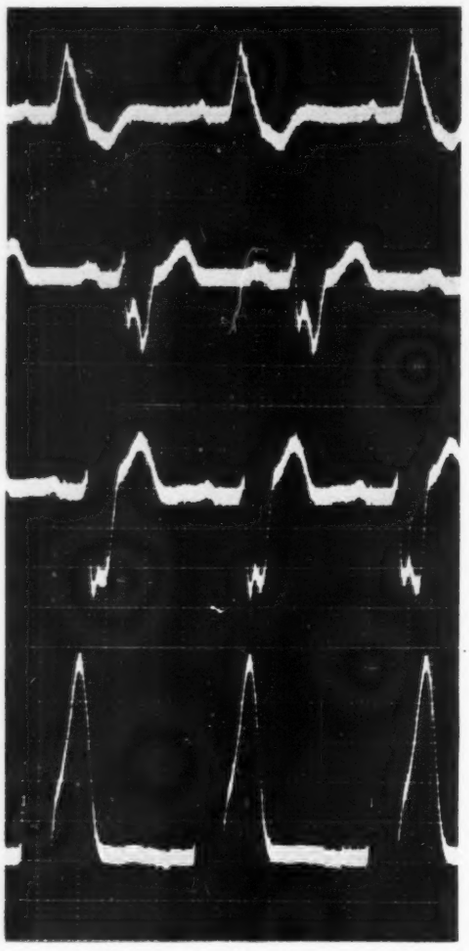


FIG. 19. P. K., a male, fifty-six, had left bundle branch block. The EKG did not change. (See also Fig. 18.)

included in this group whose "mean" arterial pressure dropped less than 20 mm. Hg and who therefore are counted as "not improved" in the previous paragraphs and tables.

The changes in diastolic pressure are analyzed separately in Table XVII.

Of 406 patients whose initial diastolic pressure was 100 mm. Hg or more 388, i.e., 96 per cent, had a decrease of 1 to 62 mm., average 18 mm., whereas only eighteen patients, i.e., 4 per cent, had an increase of 1 to 22, average 7 mm.

It has been assumed that the lowest blood pressure figure obtained after 0.6 Gm. sodium amytal indicates the maximum decrease which could be expected in the individual patient from any form of treatment. Figure 7 shows in three typical charts that the blood pressure values obtained without sodium amytal after rice diet may be far lower than the lowest values reached during the sodium amytal test before the diet.

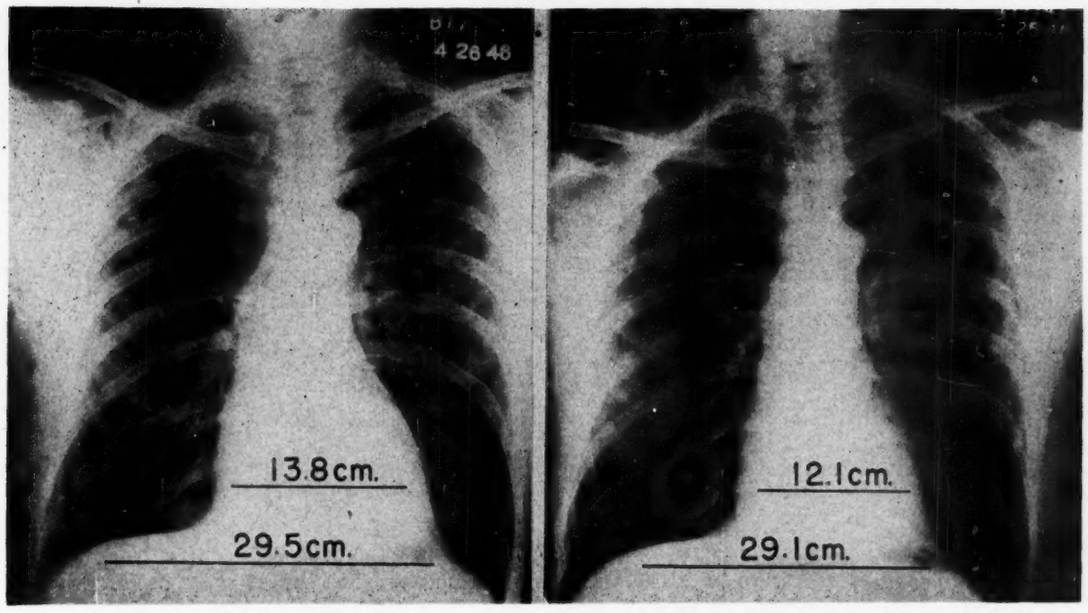
*Heart Size.* The assumption that cardiac enlargement in hypertensive vascular disease is desirable in order to overcome the increased peripheral resistance has been a pious self-deception of the physician who had no means of influencing the disease and preventing the progressive cardiac breakdown.

Cardiac enlargement in hypertensive vascular disease has been found to disappear when the patient is given the rice diet. Chest films taken before and after rice diet show decreases in the heart sizes with changes in the transverse diameter up to 30 per cent. Decrease in heart size does not necessarily coincide with decrease in blood pressure. In a number of patients whose blood pressure remained at a constant high level or showed only an insignificant reduction, a considerable decrease in heart size was found. (Figs. 14 and 15.)

Six foot chest films of 286 patients taken before and after one month or more of dietary treatment (no digitalis or other drugs) are available for comparison. Table XVIII combines the averages of the measurements of the transverse diameter of the heart and of the chest diameter grouped according to the extent of change.

Before the rice diet the transverse diameters of the hearts of the 286 patients ranged from 10.2 to 19.4 cm.; the average was 14.2 cm. After the rice diet they ranged from 9.4 to 18.2 cm.; the average was 12.9 cm.

In 15 of the 286 patients (5 per cent) the heart became larger. In these patients the transverse diameter of the heart showed an average increase of 2.6 per cent. The chest diameter (average) increased by 0.8 per cent. The average period on the diet was




A B

FIG. 20. A and B, C. O. a male, forty-three years of age, had hypertensive vascular disease of ten years' duration, left bundle branch block and dyspnea. Total PSP excretion in two hours, 57 per cent. Rice diet was started May 4, 1946, and strictly followed (10–11 mg. Cl per 100 cc. of urine). No medication was given. The patient became asymptomatic. There was a decrease in blood pressure and reduction in heart size with change in transverse diameter of 14 per cent. (Fig. 21.)

184 days. The average heart size in this group before treatment was the smallest found.

In 271 of the 286 patients (95 per cent) the heart became smaller with an average change in the transverse diameter of 10.6 per cent. The chest diameter decreased by 0.6 per cent (average). The average period on the diet was 118 days.

Figures 8 to 15, 17, 18, 20 show typical changes in the heart picture produced by the rice diet.

*Electrocardiograms.* The blood supply to the heart muscle will be inadequate whenever the coronary blood flow is decreased without a simultaneous decrease in the myocardial energy requirements, or whenever the myocardial energy requirements are increased without a simultaneous increase in the blood supply through the coronaries. In either case the effects of the deficiency in oxygen and nutrient substances, with the resulting chemical changes and consequent clinical manifestations, are easily predictable.[7,28] The natural course of these events is recorded by the electrocardiographic findings which indicate advancing myocardial impairment: left axis deviation, $T_1$ inversion, arrhythmias, conduction defects or myocardial infarction.

An attitude of resignation has prevailed with regard to the abnormal electrocardiogram in hypertensive heart disease. "It is a pertinent feature of records denoting left ventricular strain that the changes are slow in their evolution and more or less permanent once they have appeared."[29] "When once established the T-wave and the RS-T defects described persist and remain unaltered until the death of the patient."[30]

Electrical axis and $T_1$ waves were studied in the electrocardiograms of 310 patients with hypertensive vascular disease before and after the rice diet. None of these patients received digitalis or any other drug. All electrocardiograms were made with the patient at rest in a recumbent position. The period between the two electrocardiograms compared was one month to thirty-three months, an average of six months. In 18

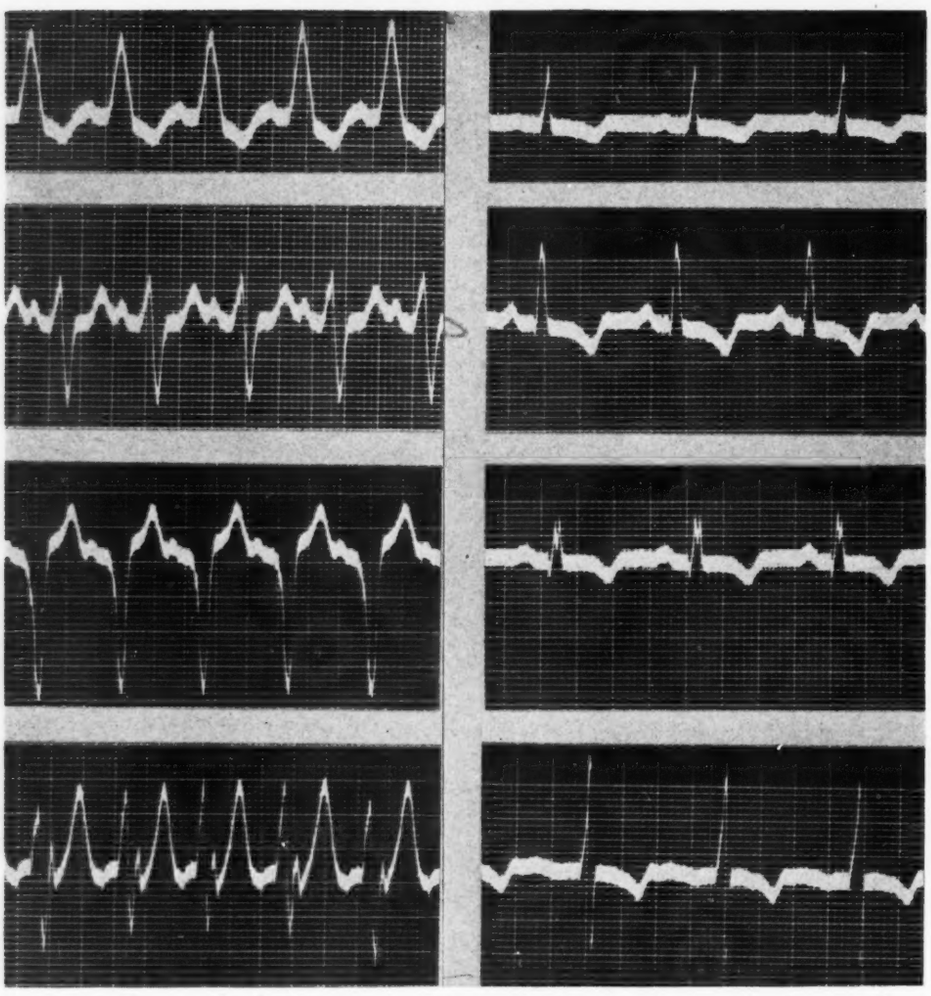


FIG. 21. C. O., a male, forty-three years of age, had hypertensive vascular disease of ten years' duration and dyspnea. April 29 to May 8, 1946: blood pressure, average, 179/126; total PSP excretion in two hours, 57 per cent. Rice diet was started May 4, 1946, and strictly followed (10–11 mg. Cl per 100 cc. of urine). No medication was given. July 24 to July 25, 1946: blood pressure, average, 157/110.———The patient became asymptomatic and there was disappearance of left bundle branch block. (Fig. 20.)

of the 310 patients the electrical axis could not be evaluated. In the remaining 292 patients the angles of the electrical axis were:

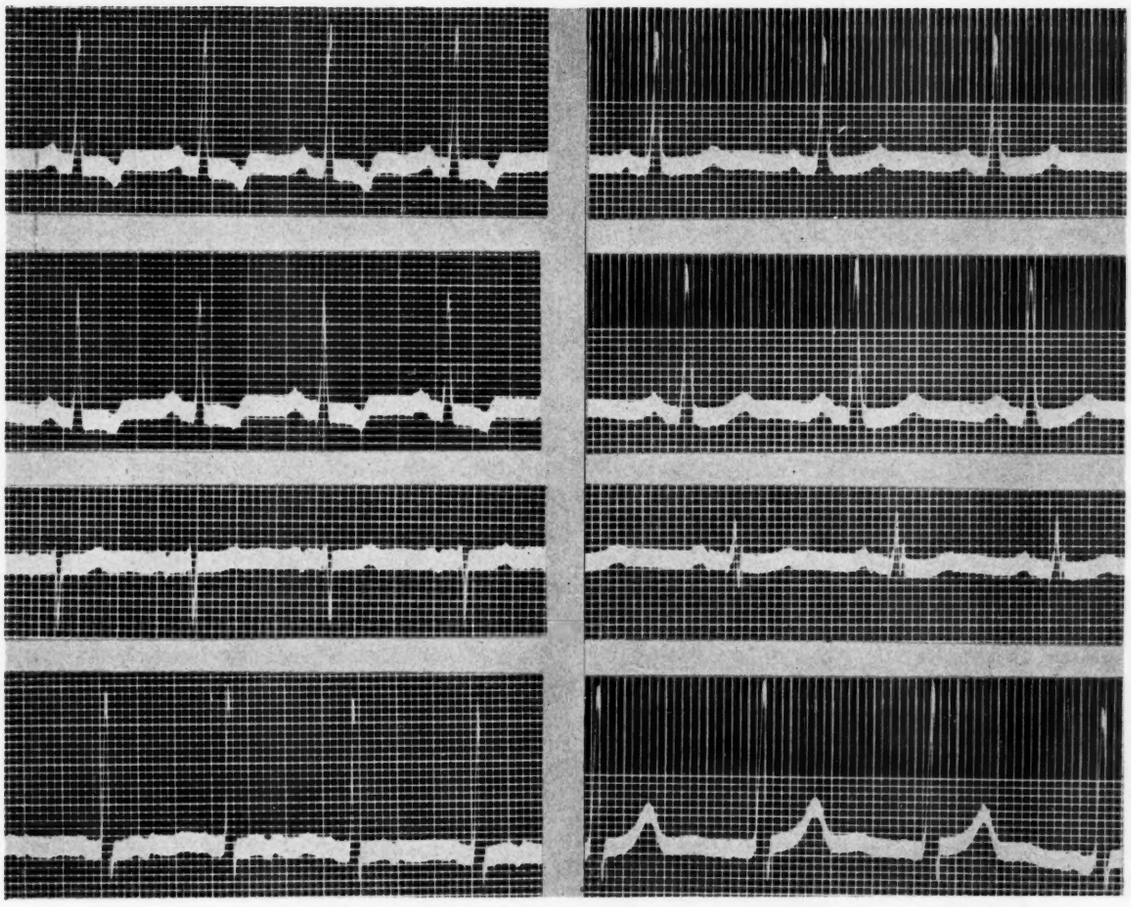
| | Before Diet | After Diet |
|---|---|---|
| More than +30 degrees..... | in 89 patients | in 131 patients |
| 0 to +30 degrees.... | in 97 patients | in 91 patients |
| Less than 0 degrees... | in 106 patients | in 70 patients |

The changes in the angle of the electrical axis of these patients are summarized in Table XIX.

Of the 119 patients whose electrical axis changed more than $\pm 14°$ during the treatment 7, i.e., 6 per cent, showed a decrease; 112, i.e., 94 per cent, showed an increase in the angle of the electrical axis.

The T waves in lead I were evaluated in 310 patients. Before the rice diet was started $T_1$ was normally upright or low upright in 165, diphasic or inverted in 145 patients. The changes during the treatment are shown in Table XX.

In seven patients there was a change of $T_1$ in the direction from upright to inverted. In 89 patients there was a change of $T_1$ in the direction from inverted to upright. In



A B

FIG. 22. A and B, R. L., a male, twenty-three years of age, had hypertensive vascular disease of three years' duration with advanced retinopathy; total PSP excretion in two hours: 2.5 per cent. No digitalis was given. Rice diet was started on December 18, 1945. Blood pressure, average, December, 18 to December 24, 1945: 222/148; January, 15 to January 21, 1946: 153/112. March, 11 to March 22, 1946: 134/94.———Inverted $T_1$ became upright within one month. The lowest blood pressure was reached two months later. (Figs. 3 and 30.)

ninety-nine patients the $T_1$ waves were completely inverted before treatment. In thirty of these ninety-nine patients $T_1$ became upright with the diet. In no patient did the reverse occur.

Excluding the patients who at the start of the rice diet already had an inverted $T_1$ (and in whom there could be no further change for the worse according to the grouping of Table xx), the percentage of those changing for the worse during the rice diet was three. Excluding the patients who at the start of the diet already had an upright $T_1$ (and in whom there could be no further improvement according to the grouping of Table xx), the percentage of those changing for the better was fifty-two.

The shortest time in which an inverted $T_1$ became normally upright was one month. (Fig. 22.) The average was ten months. In the patient whose EKG is shown in Figure 23 it took three years.

Of the 292 patients in whom it was possible to evaluate the changes both in electrical axis and in $T_1$, eighty-seven patients (30 per cent) had an initial electrical axis above $+10°$ and an upright $T_1$. Of these eighty-seven patients 7 (8 per cent) showed a change for the worse in that the electrical axis decreased below $+10°$ and/or $T_1$ became diphasic; 80 (92 per cent) did not change with the rice diet.

Of the 292 patients 205 (70 per cent) had an initial electrical axis below $+10°$ and/or

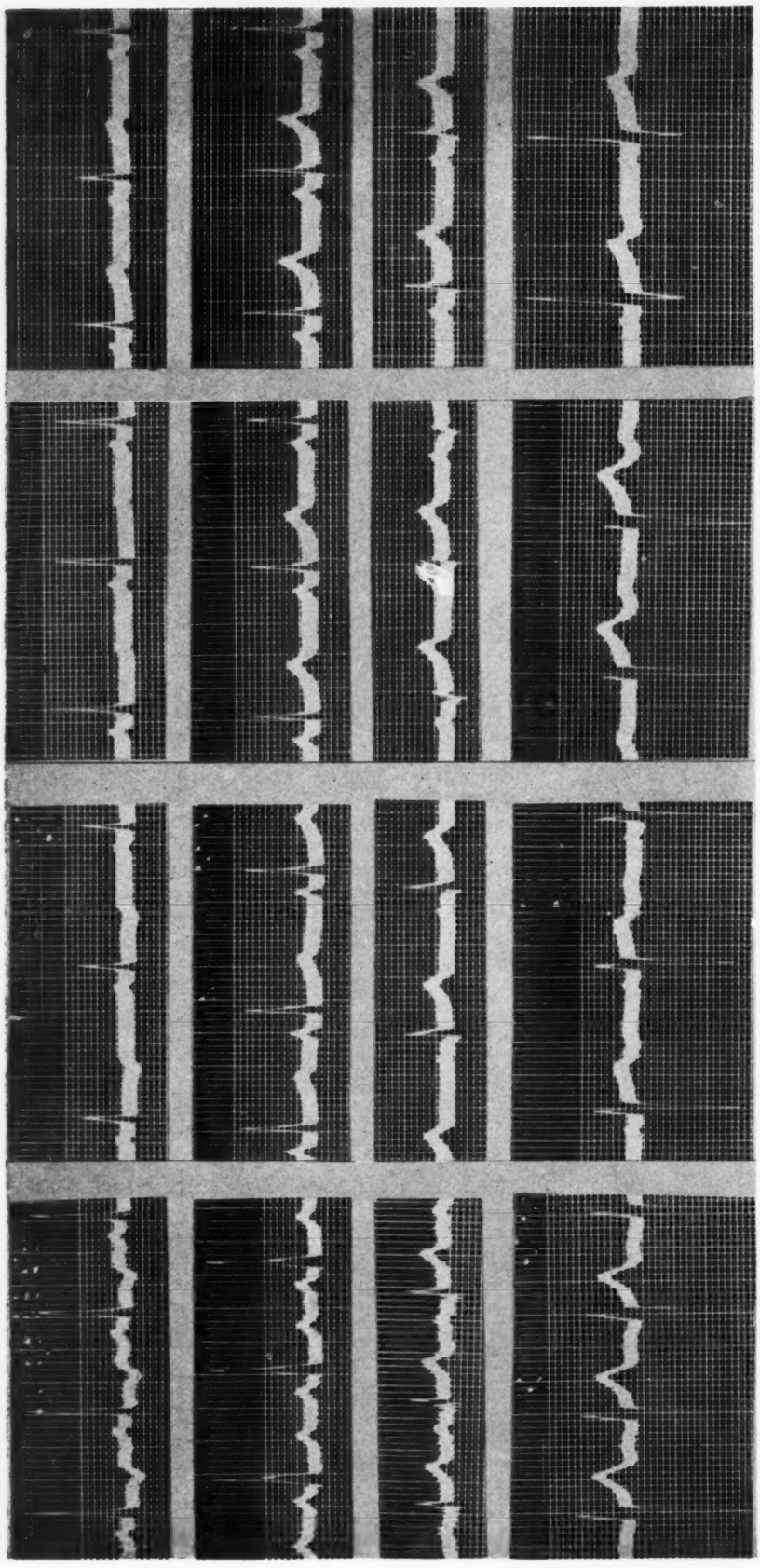
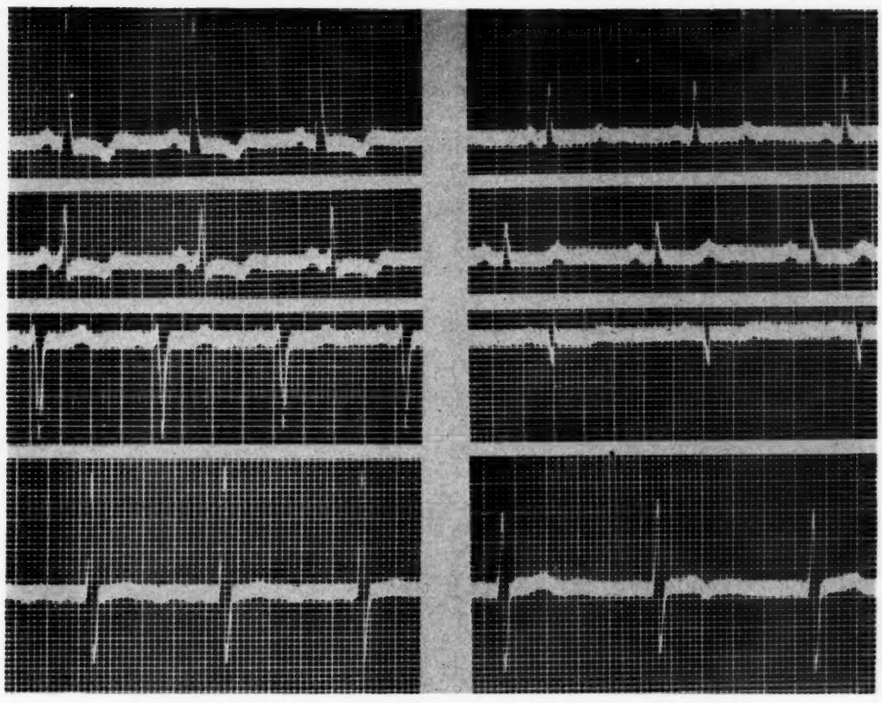


FIG. 23. A. [E. H., female, thirty-six years of age, had hypertensive vascular disease of one year's duration. Chronic pyelonephritis was present. There were severe headaches and retinal hemorrhages and "silver wire arterioles." Previous treatment with salt-poor diet; no digitalis was given. Total PSP excretion in two hours: 9–25 per cent. Rice diet was started April 13, 1943: it was moderately well followed. No medication was given. Patient was asymptomatic and working. Blood pressure averages: April 5 to April 26, 1943: 223/149; March 8 to March 10, 1944: 116/92; Feb. 20 to March 3, 1945: 159/109; May 23 to May 29, 1946; 118/79. Inverted $T_1$ has become normally upright three years after decrease of blood pressure.



A B

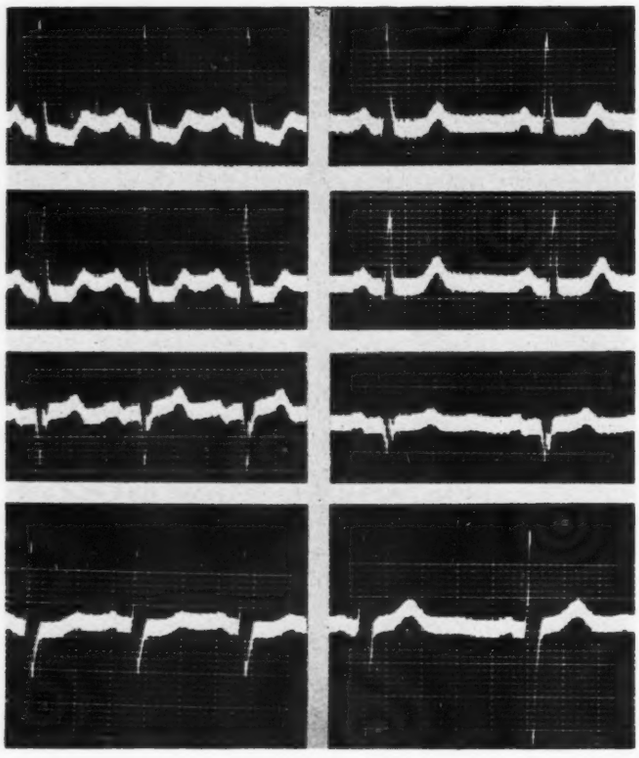
FIG. 24. A and B, C. G., a male, forty-nine years of age, had hypertensive vascular disease of two years' duration with severe headache. Two strokes occurred in 1944. He was treated with sedatives; was given no digitalis; April 6 to April 22, 1945: blood pressure average, was 196/105; total PSP excretion in two hours: 48 per cent. Rice diet was started April 24, 1945: it was followed strictly (5–20 mg. Cl per 100 cc. of urine). October 8 to October 11, 1945: blood pressure average was 136/80.———There was a decrease in the blood pressure and an increase in the angle of electrical axis. Inverted $T_1$ became upright.

a diphasic or inverted $T_1$. Of these 205 patients 119 (58 per cent) remained unchanged; eighty-six patients (42 per cent) showed an increase in the electrical axis to more than $+10°$ and/or a change of $T_1$ from diphasic or inverted to upright.

*Retinopathy.* Advanced retinopathy with papilledema, hemorrhages or exudates is a danger signal in hypertensive vascular disease. "Hemorrhages associated with white spots in the retina (hypertensive neuroretinopathy) are ominous signs. Death commonly follows within a year."[31]

Vascular retinopathy has been found to disappear with the rice diet. The retinal improvement does not necessarily coincide with decrease in blood pressure. Very severe retinopathy has disappeared in patients when the blood pressure remained at a constant high level or showed only an insignificant reduction. (Figs. 27 to 29.)

Papilledema, hemorrhages or exudates, frequently in combination, were present in 140 of the 500 patients. In eighty-eight of these, eyeground photographs taken both before and after the rice diet (one to thirty months) are available for comparison. Papilledema was found in twenty-three of the eighty-eight patients. In seventeen it disappeared completely, in five partially and in one remained unchanged. Hemorrhages were found in fifty-five of the eighty-eight patients. In thirty-nine they disappeared completely, in fifteen partially and in one remained unchanged. Exudates were found in seventy of the eighty-eight patients. In forty-two they disappeared completely, in twenty-three partially and in five remained unchanged. In one of the patients in whom the exudates cleared up partially small hemorrhages occurred after a period of twelve



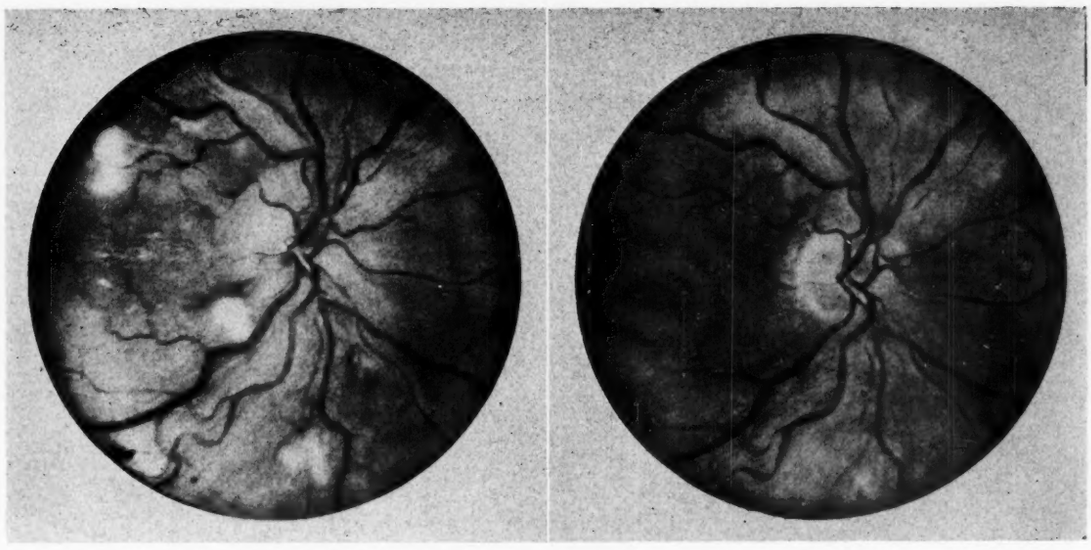
A B

FIG. 25, A and B, F. G., a female, fifty-two years of age, had hypertensive vascular disease of twelve years' duration which began in toxemia of pregnancy. There were severe headaches. She had a stroke in May, 1946. She had previous treatment in a hospital with bedrest and a reduction diet. She had been given sedatives for the last three years. No digitalis was given. August 8, 1946: blood pressure was 238/128; total PSP excretion in two hours: 57 per cent. Rice diet was started August 10, 1946; it was strictly followed for six weeks (5 mg. Cl per 100 cc. of urine). September 20, 1946 to September 26, 1946: blood pressure, average, was 150/100. There was a decrease in blood pressure._____The diphasic $T_1$ has become upright.

months on the diet (which had not been strictly followed).

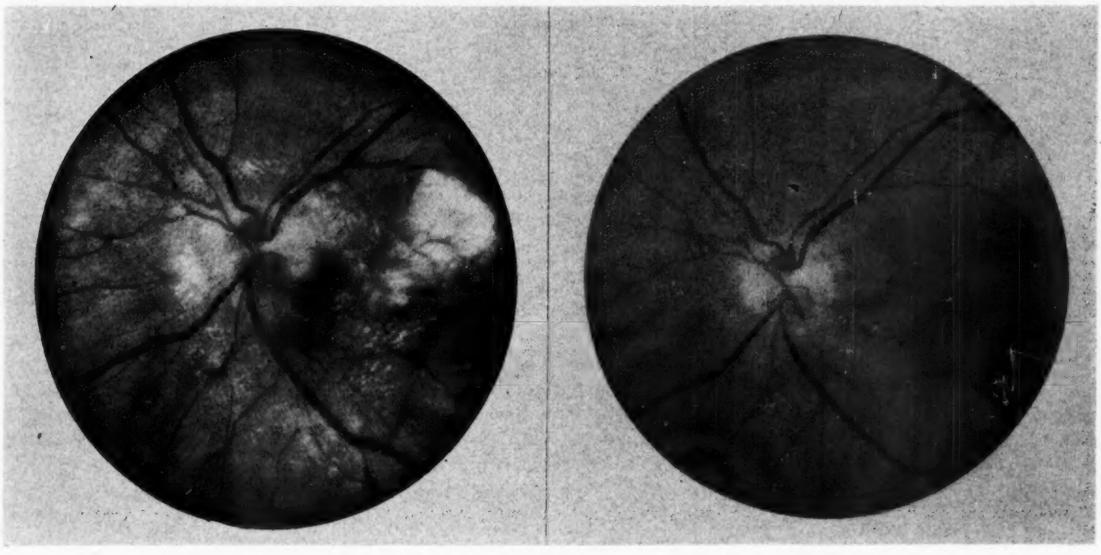
Those patients in whom the retinopathy remained unchanged had been on the diet from one to three and one-half months except for one patient with exudative stippling who was on the rice diet for nineteen months. The patients in whom the retinopathy cleared up only partially had been on the rice diet from one to seventeen months, an average of five months. The period of time in which the retinal changes disappeared completely ranged from two to thirty months, an average of fourteen months.

Figures 26 to 30 show typical eyeground photographs before and after the diet.



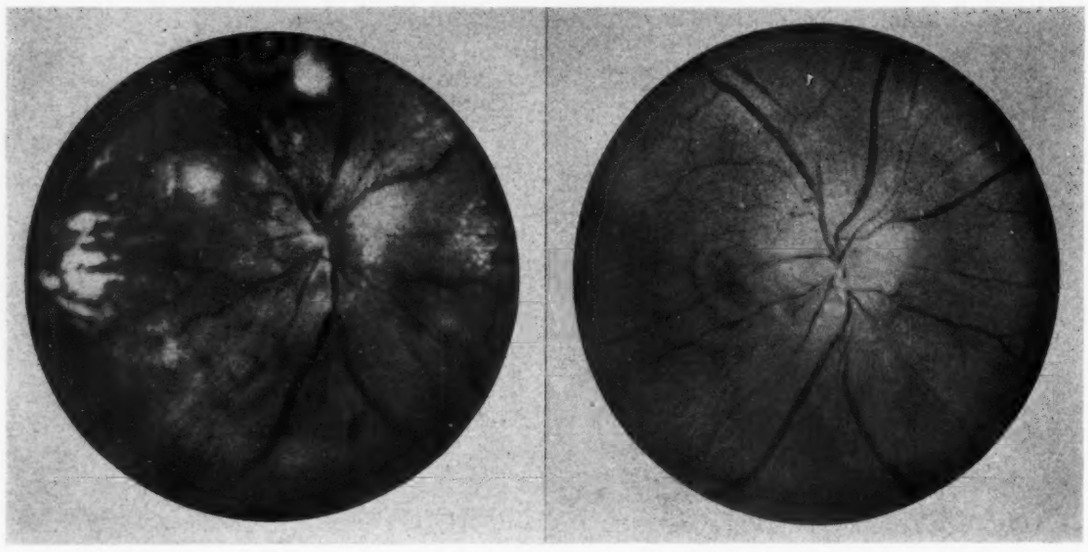
A B

FIG. 26. A and B, D. L., a male, fifty-four years of age, had hypertensive vascular disease of at least six months' duration. His previous treatment consisted of low-fat, low-protein diet and sedatives. April 19, 1946 to May 6, 1946: blood pressure average was 221/144; EKG $T_1$ inverted; total PSP excretion in two hours: 35 per cent. Rice diet was started April 26, 1946; it was strictly followed (5–13 mg. Cl per 100 cc. of urine). March 25 to March 26, 1947: Blood pressure, average, was 177/112; EKG $T_1$ was upright. September 22 to September 24, 1947: blood pressure, average, was 149/106; EKG $T_1$ upright.——————There was a disappearance of papilledema and exudates before lowest blood pressure level was reached.

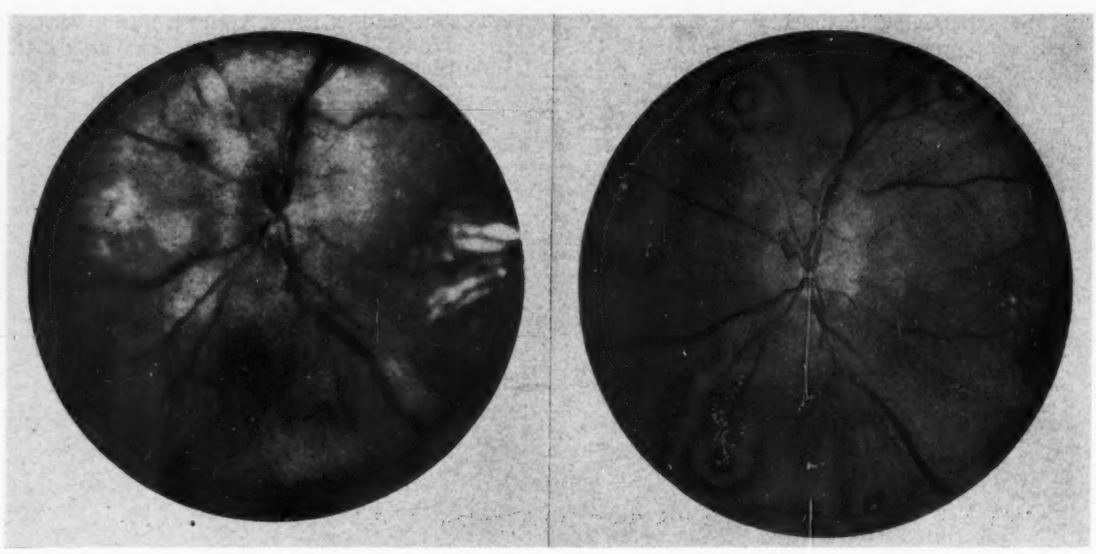


A B

FIG. 27. A and B, W. A., a male, thirty-two years of age, had hypertensive vascular disease of eighteen years' duration. Sympathectomy was performed in the Mayo Clinic in 1945. Since July, 1946, there had been progressive impairment of vision in the left eye. February 19 to February 21, 1947: blood pressure average was 255/158; total PSP excretion in two hours: 40 per cent. Rice diet was started February 21, 1947; it was moderately well followed (12–51 mg. Cl per 100 cc. of urine). September 22 to September 26, 1947 blood pressure, average 230/138.——————There was marked improvement of vision. There was a disappearance of papilledema, almost complete disappearance of hemorrhages and exudates in spite of persistence of high blood pressure.

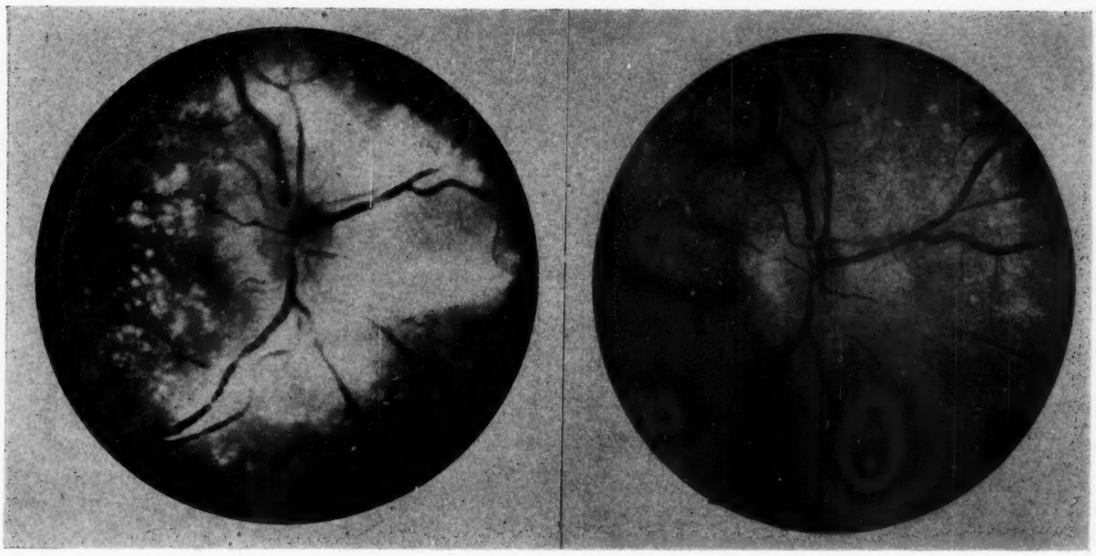


A

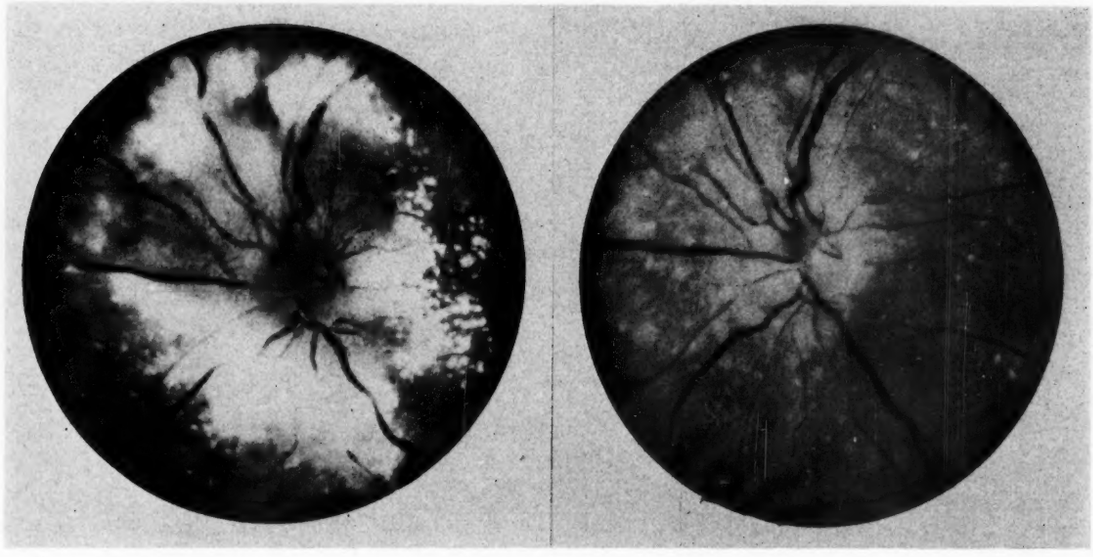


B

FIG. 28. A and B, L. W., a female, forty-five years of age, had hypertensive vascular disease of at least four months' duration. July 16 to August 5, 1944: blood pressure, average, 225/153; total PSP excretion in two hours, 59 per cent. Rice diet was started July 23, 1944 and strictly followed (4–24 mg. Cl per 100 cc. of urine). August 8 to August 13, 1945: blood pressure, average, 215/138._____There was a disappearance of papilledema, hemorrhages and exudates in spite of persistence of high blood pressure.

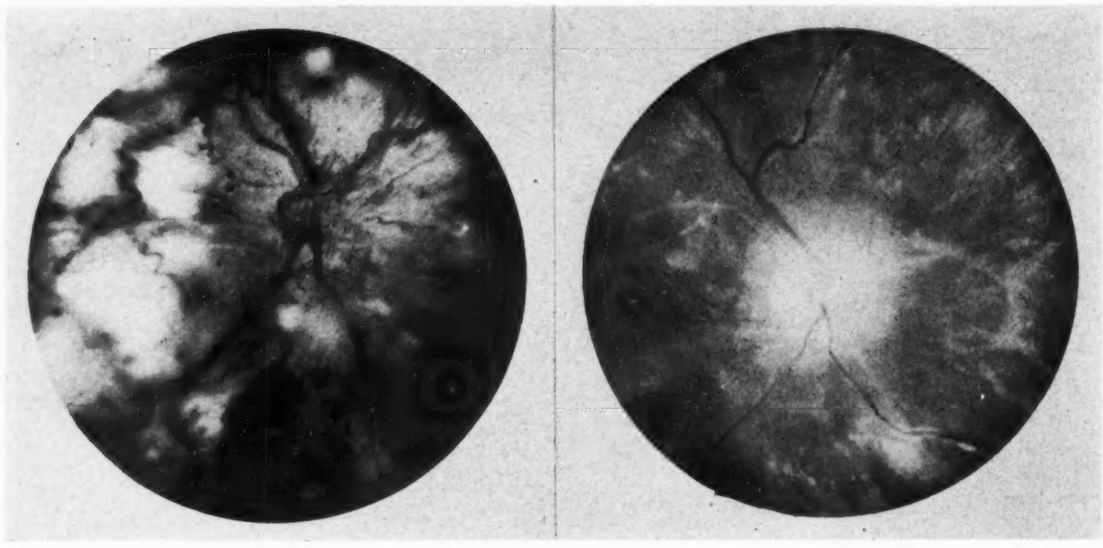


A

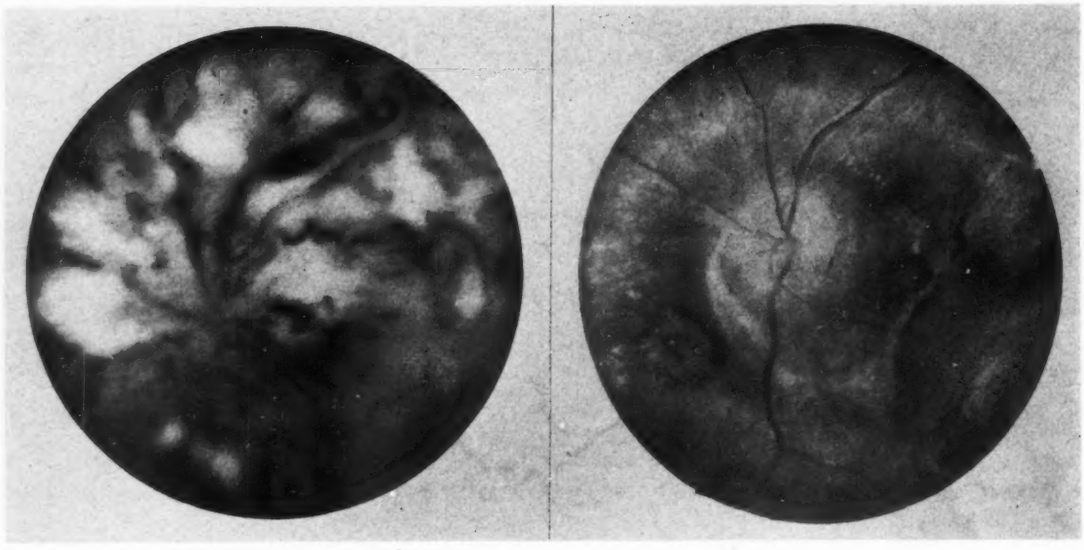


B

FIG. 29. A and B, A. McA., a male, thirty-eight years of age, had hypertensive vascular disease of at least one years' duration. He was previously treated with sedatives and low-salt diet. December 8 to 20, 1945: blood pressure, average, 216/132; EKG $T_1$ inverted; total PSP excretion in two hours, 58 per cent. Rice diet was started, December 13, 1945 but was not strictly followed (28–55 mg. Cl per 100 cc. of urine). May 5 to 8, 1947: blood pressure, average, 208/123; EKG $T_1$ upright. Papilledema, hemorrhages, exudates disappeared in spite of persistence of high blood pressure.



A



B

FIG. 30. A and B, R. L., a male, twenty-three years of age, had hypertensive vascular disease of three years' duration. Previous treatment consisted of a "modified rice diet." December 18 to December 24, 1945: blood pressure, average, 222/148; EKG $T_1$ inverted; total PSP excretion in two hours, 2.5 per cent; NPN 79 mg. per 100 cc. blood; cholesterol 340 mg. per 100 cc. serum. Rice diet was started December 18, 1945 and strictly followed for three months (8–21 mg. Cl per 100 cc. of urine). March 11 to 22, 1946: blood pressure, average 134/94; EKG $T_1$ upright. After March, diet was poorly followed (192–255 mg. Cl per 100 cc. of urine). August 15 to 21, 1946 and October 2 to 5, 1946: blood pressure, average, 194/133; EKG $T_1$ upright; NPN 60 mg. per 100 cc. blood; cholesterol 173 mg. per 100 cc. serum._____There was a disappearance of papilledema, hemorrhages, exudates and no recurrence of retinopathy although diet was broken and hypertension recurred.

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# Low Salt Diets and Arterial Hypertension*

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It is difficult to discuss the effect of diets low in salt upon the blood pressure and subsequent course of patients suffering from arterial hypertension of unknown cause without first examining the condition itself and its fundamental nature. So little is known of its etiology and mechanism that the attitude one adopts becomes a matter of belief based on the scant evidence available. One idea is that etiologic factors in all cases of arterial hypertension are the same; that similar interacting influences, or disturbances, lead to an altered vascular physiology expressed by hypertension. This view is untenable. Four simple mechanical factors act to maintain a normal blood pressure as well as a high one; i.e., the volume of blood, its viscosity, the function of the heart and the resistance to blood flow in the periphery. Many others affecting not only the cardiovascular system, but general and apparently unassociated bodily functions, may express their actions by changes in blood pressure. In fact, the blood pressure can be considered as a resultant of a number of interacting influences, and can become decompensated in a number of ways. Some of these are well understood but many are not. It may be as untrue to state that all cases of arterial hypertension have the same basic disturbance as it is to state that all patients with fever have the same etiologic agent.

Another theory is that patients with pathologic conditions associated with hypertension, and to which hypertension is considered secondary, may have different etiologies and mechanisms depending upon the disease present. All other patients with conditions not associated with these known diseases are considered to have "essential" hypertension. A similar etiology and mechanism is, therefore, postulated for such subjects. This is the prevailing viewpoint at present. With this theory goes a tacit assumption that diagnostic methods are accurate enough to differentiate obscure underlying conditions. The mechanism of the elevation of blood pressure of most patients in this category may well be a uniform one, but the assumption of a common etiology cannot be made at this time.

The third point of view, so aptly expressed by Fishberg,[1] is that so-called "essential" hypertension is a "collective concept for a number of conditions having in common the positive characteristic of arterial hypertension and the negative one of the absence of primary renal disease." On this theory, it becomes possible to consider that a number of different pathologic conditions are being grouped as a syndrome in which various disturbances lead to elevation of the blood pressure with its concomitant cardiovascular and renal changes. Furthermore, when therapeutic results are obtained in some individuals but not in all, one can examine them according to their actions on these different disturbances and not accept or discard them in the light of one mechanism only. In the following discussion, the possibility that we are dealing with several different conditions having a common clinical finding should be borne in mind.

## SODIUM CHLORIDE AND ARTERIAL HYPERTENSION

Any relationship which may exist between salt (sodium, chloride or both) and arterial hypertension is a complex one. To break it down into its component parts, one

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must consider the various interacting influences which may be at work. The question of whether or not there is a disturbance of sodium chloride balance in hypertension can only be answered by examining ways in which such a disturbance could act, for the evidence on this point is far from clear.

The kidneys are the first organs to be considered. Is there a specific retention of sodium chloride by hypertensive kidneys? Little is known of the effect on these ions of mild renal vascular disease or constriction. In right-sided heart failure, for example, the clearance and the excretion of salt are reduced.[2,3] In hypertension Ambard and Beaujard[4] postulated a "dry retention" of salt and advocated for the first time a salt-poor diet to counteract it. Later, Ambard abandoned this idea, but many others continued to entertain it. Recently, with the present revival of interest in the subject, Perera[5] showed that hypertensive patients placed on twenty-four hours of rigid salt restriction did not lose weight or water, while normal individuals did. Both groups lost the same amount of salt, but in two pairs of subjects the clearance of sodium chloride was reduced in the hypertensives. Farnsworth,[6] on the other hand, studying the renal excretion of chloride, found that chloride clearances were increased in hypertensive patients and that the renal tubules demonstrated a specific failure to reabsorb this ion. Furthermore, Selye[7] recently reported that some hypertensive patients with high diastolic pressures showed an increase in blood sodium relative to chloride. She believes that this is the result of the action of the adrenal cortex. These findings do not support Ambard's original idea of "retention chlorurée sèche."

If there has not been demonstrated a specific renal diminution of salt excretion, one must examine those factors which can influence the kidney to retain salt and relate their activities to what is known about hypertension. Among them are: (1) the relation of the adrenals to salt balance; (2) the relation of the adrenals to hypertension; (3) the relation of other influences to the adrenals and (4) the relation of salt to hypertension.

*Salt and the Adrenal.* The relation of sodium chloride balance to the adrenal cortex is well known. Steroid compounds similar to those of the adrenal are specific for counteracting the derangements in sodium balance found in adrenal insufficiency. The loss of sodium chloride in Addison's disease is the predominant, though not the only, disturbance which accounts for the symptoms and findings. Disturbances of electrolytes do occur in some cases of adrenal cortical hyperfunction, with increases in the blood levels of sodium and decreases in potassium.[8a] Rats reared on a low sodium diet excrete radioactive sodium more rapidly than normal rats,[8b] and a diet free of sodium has been said to produce changes in the adrenals.[8c] The action of the adrenal cortex and of desoxycorticosterone on salt balance is thus an established fact, although there are still many important questions to be answered concerning its method of acting and its relation to other organs and systems.

*Adrenal Cortical Factor in Hypertension.* Any discussion of the rôle of sodium chloride in arterial hypertension must involve the part the adrenal glands play in this condition. About this there is considerable controversy. Evidence for an adrenal factor, and particularly an adrenal cortical factor, in arterial hypertension is suggestive but not thoroughly convincing. It is obvious that the adrenal cortex is necessary for maintenance of an elevated blood pressure. It is also necessary for maintenance of a normal blood pressure. Bilateral adrenalectomy will prevent the development of experimental hypertension and lower the blood pressure in one already established unless substitution therapy is used. But other conditions, sometimes disregarded, are just as necessary as mentioned previously. Even a normal body temperature may be required, for an elevated blood pressure may fall during bouts of fever induced by disease or by the introduction of pyrogens.[9]

A conclusion that the adrenal cortex is necessary for hypertension to be established does not necessarily implicate this organ as being primarily involved. In some cases it may be, however. Hypertension, associated with Cushing's syndrome, can apparently result from tumors or hyperplasia of the adrenal cortex. In this condition one is drawn to the conclusion that an adrenal mechanism plays a primary or initiating rôle. Small adenomas of the adrenal cortex have been described in about 1.45 per cent of all autopsies; patients showing these tumors frequently exhibited hypertension in life.[10] Hyperplasia of the cortex, associated with hypertension, has also been described.[11] These findings have been doubted.[12] It is possible that these cases represent a different type of the condition, although so far no attempt has been made to classify them accurately on clinical grounds. Heinbecker,[13] however, believes that an adrenal-pituitary-renal relationship is disturbed in arterial hypertension, resulting in pituitary changes and renal ischemia.

Measurements of the urinary excretion of cortical-like and other steroids have not offered proof that these substances are abnormal in cases of hypertension even if values are low.[12] Total amounts of 17-ketosteroids or other steroid metabolites may give misleading information concerning the activity of the adrenal cortex, unless the values found are well outside the normal (and fairly wide) range. All cortical steroids and their metabolites are not measured by this method. If there is any suggestion to be gained from such studies, it is that the cortex may be underactive.

More direct and exact measurements of these substances have yielded interesting evidence that some disturbance of the adrenal cortex or of the body's ability to metabolize steroids may be present in some cases of hypertension. Recently, Dobriner[14] reported the presence of a metabolite of adrenal cortical steroids $\Delta^9$, etiocholenalone, in the urine of half of six patients with hypertension. These were all women. It was also present in two normal subjects, one male and one female, out of twenty-eight and in twenty-five of twenty-six patients with carcinoma, excluding that of the breast. It was present in five of seven subjects with Cushing's syndrome as well. Another so far unidentified metabolite occurred in the urine of all of five hypertensive women and in only two of nine normal subjects. These findings suggest that alterations in the metabolism of adrenal cortical steroids occur in some cases of arterial hypertension and Cushing's syndrome. Dobriner's careful analyses, and time-consuming methods of extraction and identification of minute quantities of steroids from large volumes of urine are inapplicable to the usual research laboratory. It is hoped that more rapid and simple methods for the study of these compounds may be developed in order that they be correlated further with special varieties of hypertension and other diseases.

Goldblatt,[15] in his recent excellent review, states, "Of the endocrine organs, the only one that may possibly play a significant, even if only a secondary part (in hypertension) is the adrenal, although this conclusion is contested on basis of inadequate evidence." Newer evidence does not yet controvert this viewpoint. Until the disease with its secondary manifestations can be consistently reproduced by disturbing adrenal function, evidence that the adrenals are implicated as primary etiologic agents in most patients must be considered inadequate. If they are concerned, it is uncertain whether their secretions are increased or diminished.

*Relation of Salt and Desoxycorticosterone Acetate to Hypertension.* The relation of salt to hypertension is a matter of controversy. Most of the evidence for salt being important comes from studies on patients using low salt diets which will be discussed later. There is accumulating evidence, however, that at least under some conditions sodium chloride, taken in large amounts, may adversely affect the blood pressure of hypertensive patients more than of normal ones. A high salt intake may reverse the hypoten-

sive action of low salt diets.[16] The treatment of Addison's disease by desoxycorticosterone acetate and salt is often accompanied by a rise in blood pressure to levels over 140 mm. Hg systolic and 90 diastolic, sometimes reaching diastolic levels of 100 to 110.[17,18] When desoxycorticosterone acetate and salt were given to normal subjects a small but significant rise in blood pressure occurred after two to three weeks. When the same amounts were given to patients with hypertension, the blood pressure became higher in one to four days.[19]

Experimentally, the blood pressure of rats and dogs can be elevated by the administration of salt and desoxycorticosterone acetate, and renal vascular lesions have been reported to occur.[20] That desoxycorticosterone acetate and salt will elevate blood pressure appears to be an established fact, not only in animals, but in human beings as well. The administration of large amounts of salt alone, however, to normal subjects, does not change blood pressure.[21] Plasma volume and venous pressure may, in some cases, become considerably elevated after salt, with extracellular water, measured by "thiocyanate space" increased and much sodium retained.

Landis[22] recently reported some interesting observations on hypertensive rats. Choices of sodium chloride and other electrolytes were offered to three groups of animals: normal, moderately hypertensive and severely hypertensive. Those exhibiting moderate hypertension ingested significantly less salt than did the other groups. One implication of these results is that there may be some dysfunction of certain functions of the adrenal in these animals.

These experiments do not incontrovertibly support the idea that the adrenal cortex is disturbed in hypertension. They merely show that experimental alterations in salt balance may affect blood pressure when desoxycorticosterone acetate is used. These results have not been duplicated by the administration of whole cortical extract.[8] Furthermore, the adrenalectomized animal and human being seem to be more susceptible to the hypertensive actions of these substances than are normal ones. This has led Soffer[8a] to suggest two vascular regulating factors of opposite action in the adrenal cortex which may be disturbed in hypertension and which are present in whole gland extracts. One of these may be similar to desoxycorticosterone acetate. The other may be diminished in hypertension and absent after adrenalectomy. If desoxycorticosterone acetate can act as a pressor or vasoconstrictor substance, this would be important in some cases of hypertension.*

*Relation of Other Influences to the Adrenals and Kidneys.* It is not within the province of this discussion to consider the complex interrelations between the adrenal cortex and other endocrine organs. There are three influences, however, which should be mentioned. The first concerns the work of Marshall and Kolls[23] who found that in dogs extirpation of one adrenal resulted in markedly increased excretion of chloride and water by the homolateral kidney, while the excretion of creatinine was unaffected. This suggested that the change was independent of renal blood flow. The same effect was observed after unilateral section of the splanchnic nerve and Marshall concluded that the results were due to nervous influences. It is probably impossible to remove a dog's adrenal without severing many of the sympathetic nerves which lie in a plexus about the gland and thus partially denervating the kidney. These experiments suggest the presence of a nervous (or hormonal) influence on the renal excretion of chloride which is not humoral. The converse, i.e., that stimulation of sympathetic nerves leads to salt retention, has not been demonstrated.

The second influence concerns the recent demonstration by Vogt[24] directly and by

* Since this manuscript was prepared, desoxycorticosterone acetate has been found to elevate the blood pressure of hypertensive patients when it is injected intravenously. It does not change the blood pressure of normal individuals. Similar compounds, i.e., progesterone, dehydroisoandrosterone acetate, $\Delta^5$ pregnenolone, testosterone and whole adrenal cortical extract (Upjohn) did not significantly affect blood pressure.[37]

Long[25] indirectly that epinephrine is a potent stimulus to adrenal cortical secretion. Of great interest to this problem is the finding that "stimulation of the sympathetic nervous system and consequent liberation of epinephrine is capable of increasing

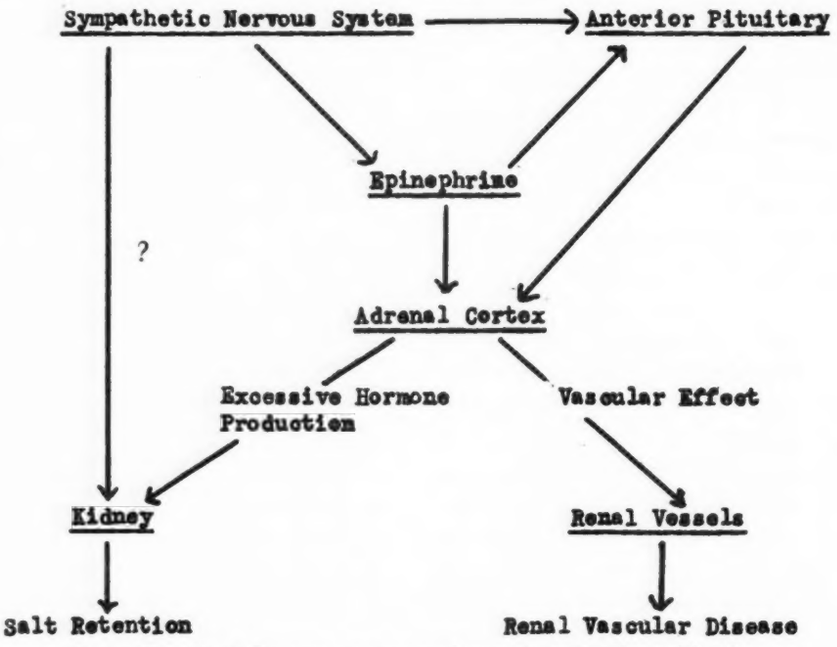


FIG. 1. Possible influences on the renal retention of sodium chloride.

cortical hormone output."[25] If hyperactivity of the sympathetic nervous system can cause the adrenal cortex to liberate salt-retaining hormone, which has not yet been shown, a mechanism is provided for salt retention in hypertension. There seems to be evidence that overactivity of the sympathetic nervous system may play a part in some cases of "essential" hypertension, although perhaps not in all.

If one were to attempt to diagram these influences in order to clarify them, a scheme such as Figure 1 would result. Of course, these effects have been demonstrated experimentally only and have not been confirmed in human beings.

## EFFECT OF LOW SALT DIETS ON HYPERTENSION

Ambard and Beaujard[4] were probably the first to recommend a salt-poor diet for the treatment of hypertension. Later Allen and Sherill[26] strongly advocated this measure as did Volhard.[27] Other investigators have obtained effects with this diet and various theories have been proposed to account for them, while many others were not convinced of its efficacy. Diets of this type came into rather wide use in Europe but were not generally applied in this country. Recently, however, a renaissance of this subject has occurred (Table 1), principally because of the work of Kempner.[28] By applying a diet of rice, fruit juices and vitamins to the treatment of hypertension, he found consistent and significant reductions in blood pressure in about 57 per cent of patients. This diet contains less than 200 mg. of sodium. Recently, Grollman et al.[16] studied six patients on a diet containing less than 1 Gm. of sodium chloride. A significant fall in blood pressure occurred in two, with slight reduction in three others.

Probably the most complete work on the subject was done by Viersma.[29] His experiments appear to be the most extensively controlled and deserve attention. He studied eight patients suffering from so-called "essential" hypertension, two from chronic nephritis and four from malignant hypertension. Observations on one patient ex-

tended for more than two and one-half years. His control periods were long and carefully standardized. In seven of the ten patients with "essential" hypertension or that secondary to chronic nephritis, blood pressure became lower under the influence of a diet containing less than 1 Gm. sodium chloride per day. Viersma concluded, however, that the decline was not great, the systolic pressure falling 40 mm. Hg or less and the diastolic 26 mm. Hg at the most. Ingestion of this diet was associated with oliguria but had no demonstrable effect on renal function except in one subject. In this instance, low grade uremia became worse when treatment with ammonium chloride and salyrgan produced a sodium chloride deficiency. The diastolic pressure decreased further when this occurred. In cases of malignant hypertension the salt-poor diet had little effect on blood pressure. In general, but with exceptions, he found that changes of blood pressure during salt retention or loss paralleled changes in blood volume although variations were relatively small. He also noticed that changes in blood pressure lasted for a long period after return to a normal diet.

Viersma found no reasons in his own work and in an extensive review of the literature to assume the existence of any abnormalities of sodium chloride metabolism in "essential" hypertension. In the malignant stage, however, even when renal function was good, he found that salt was lost by the kidneys. He did not believe that the adrenal cortex was involved in the effects noted, but that they occurred because of a decreased cardiac output resulting either from a change in blood volume or from some reduction in peripheral and elastic resistances.

TABLE I

SUMMARY OF RESULTS REPORTED IN THE RECENT LITERATURE

| Author | Type of Diet or Sodium Content mg. | No. of Patients Treated | (O) Outpatients; (H) in Hospital | No. Affected Favorably | Change in Diastolic Pressure mm. Hg | Per Cent Afflicted | Remarks |
|---|---|---|---|---|---|---|---|
| Bryant and Blecha[30] | 200 | 45 | O | 26 | >30 | 18 | |
| | | | | | >20–29 | 40 | |
| Kempner[28] | Rice | 47 | H | 25 | >20 | 53 | Renal disease primary |
| | (200) | 50 | H | 20 | >20 | 40 | Renal disease secondary |
| | | 65 | H | 12 | >20 | 18 | Renal disease absent |
| Grollman et al.[16] | 200 | 6 | H | 2 | >20 | 33 | |
| Filipse and Filipse[35] | 200 | 32 | O | 13 | >20 | 41 | |
| Viersma[29] | 400 | 8 | H | 2 | >20 | 25 | "Essential" hypertension |
| | 400 | 4 | H | 1 | >20 | 25 | Malignant hypertension |
| | 400 | 2 | H | 2 | >20 | 100 | Nephritis, chronic |
| Schroeder et al.[32] | Rice (200) | 6 | H | 1 | 20 | 17 | |
| Behrendt and Burgess[36] | Rice | 9 | H | 7 | .... | ... | Average pressures reported Diastolic change < 20 mm. |

Among others who have recently studied the effects of this diet upon the blood pressure of hypertensive patients, Bryant and Blecha[30] found a significant lowering of diastolic pressure (20 mm. Hg or more) in 57.8 per cent of patients treated with diets containing less than 200 mg. of sodium. These were outpatients and blood pressures were all ambulatory readings. Dock[31] states that about half of the patients in his series were benefited by low salt regimens.

Our own experiences, both with a diet containing 1 Gm. of sodium chloride and with Kempner's rice diet, have been disap-

pointing. Although the series was small, patients were carefully controlled in a hospital. One Gm. salt diets were found to be relatively ineffective in patients with severe arterial hypertension and were not used extensively.[33] After at least a month in the hospital on a normal diet containing salt, the institution of salt restriction was not observed to affect the blood pressure significantly when used for a period of two to eight weeks. On the other hand, decided depression of the blood pressure to normal or near normal was observed in occasional patients. For example, a forty-two year old woman with some of the signs of Cushing's syndrome showed considerable edema and a disturbance of water excretion characterized by a low urine volume which was relatively unaffected by varying the intake of fluids. Her urine contained antidiuretic substance. Coincident with the use of a diet containing 1 Gm. of sodium chloride her blood pressure fell to normal levels from approximately 220 mm. Hg systolic and 120 diastolic. Occasionally, other patients responded similarly. These were in most instances women exhibiting obesity who were often at about the age of the menopause.

Six patients were studied carefully, using the rice diet of Kempner.[32] Control periods in hospital extended for about a month in most instances. The institution of the rice diet did not change the average diastolic pressure of three patients with severe hypertension at all. In two others the fall was slight and in a third the average diastolic pressure fell 20 mm. Hg. The plasma chlorides fell in all patients, but in two in whom plasma sodium levels were followed there was little change. This was also noted by Viersma[29] and no explanation is offered. The one patient in whom the diastolic change occurred exhibited obesity, easy bruising and a reduction in tolerance to glucose. She had at one period of her life taken insulin. The administration of sodium chloride to this diet was not accompanied by consistent changes in the opposite direction as far as blood pressure was concerned. It was concluded that the rice diet had little advantage over a normal diet low in salt and that the change expected was minimal and occurred in those patients with less severe manifestations of their disease. While these studies were not as extensive as those of Viersma, the conclusions were similar, i.e., that the changes expected when the subjects are well controlled are slight. The diet is a rigorous ordeal for most patients and is hardly justified unless it can be shown to have special advantages.

It should be pointed out that adequate control periods are essential in judging the effect of any procedure upon the blood pressure in hypertension. It is an axiom that any therapeutic procedure vigorously pursued and instituted for the relief of "essential" hypertension will lower blood pressure and a corollary that nothing so far discovered is specific for the disease. We believe that the control period must be carefully evaluated and that the blood pressure must be at the lowest stable level for a considerable period of time before any procedure is instituted. Viersma studied some patients as long as three and one-half months without doing anything. The very fact of treating the patient, as well as rest and hospital routine, will often produce decided effects.

In Kempner's studies, when he found declines in blood pressure in twenty-eight of fifty patients with renal disease and in thirty-seven of sixty-five without renal involvement, control periods which we consider adequate were not indicated. In his published charts they varied from seventeen to four days, the average being nine days.[28] In Grollman's series the control periods were somewhat longer, but in no patient were these periods more than two weeks.[16] Controls in other recent studies have not been published, yet it is only by long periods of control, impossible in most general hospitals, that one can evaluate adequately therapeutic procedures of this kind. One recent study was well controlled, but the effects on the diastolic pressure did not appear to be marked.[36]

A small group of female patients has been studied who appeared to respond favorably and sometimes dramatically to a reduction of sodium chloride intake.[33] We have a clinical impression that many of these patients exhibit certain common findings which occur to a more marked degree in Cushing's syndrome. For lack of a better term, they have been called "pseudo-Cushing's."* They are usually obese with the obesity often confined to the trunk. They bruise easily and exhibit a curious mottled cyanosis of the skin especially of the extremities. They sometimes show an abnormal tolerance to glucose of a type resembling diabetes. Rarely has osteoporosis been found. There may be associated menstrual disturbances or the menopausal state. Hirsutism has occasionally been noted. The possibility exists that these subjects represent a separate disease which hypertension is associated with secondarily. If the activity of the adrenal cortex is found to be altered in these patients, their hypertension might be on that basis. On purely clinical grounds that suggestion is possible. The response of their blood pressure levels to salt restriction may indicate that salt is concerned in their hypertension.

If salt-poor diets do lower blood pressure in some cases, when psychotherapeutic influences are excluded, this must be explained. Adequate explanations are lacking. It is difficult to understand how retention of salt *per se* can raise blood pressure unless circulating blood volume is increased. The theories proposed are in the main unconvincing in the light of other and more direct evidence for different mechanisms. Grollman[34] believes that there may be some reduction in extracellular fluid resulting in a diminished plethora of the vascular system. Still, explanations of the mechanism of the lowering of blood pressure by the use of a low salt diet remains as unclear as does the inconsistency of response in different patients.

One of our patients who was put on the diet had exhibited diminution of renal function without nitrogen retention. After two weeks on the rice diet she became drowsy, disoriented and developed nitrogen retention and diminished urine volume. When her plasma chloride and sodium content were finally measured, they were at levels of 118.4 and 69.0 mEq./L., respectively. She died in uremia without significant change in the level of her blood pressure. This case is mentioned for two reasons. First of all, it can not be too strongly stressed that a low salt or rice diet can bring on fatal consequences when renal function is reduced. We have observed the same sequence of events in patients suffering from congestive heart failure after severe salt depletion from the use of mercurial diuretics. Secondly, the fact that this patient's sodium and chloride levels in plasma and presumably in her whole body were reduced markedly without change in blood pressure, suggests that sodium chloride was not concerned in the mechanism of the elevation of her blood pressure. Viersma believes that blood volume changes may account for the results observed but it is difficult to conceive of this mechanism as the principal factor. The explanation is unclear and the mechanism unknown.

It is our present belief, however, that certain patients will respond to a low salt diet with reduction in blood pressure. Some of these patients may be suffering from a disease different from that commonly considered to be "essential" hypertension. Slight changes may be observed in other patients. These are probably due to secondary influences and not primarily concerned in the mechanism of the elevation of blood pressure. On the whole, in our experience those patients with the most severe degree of hypertension respond to salt restriction least. And this is the group which it is necessary to help.

Until more is known about the subject it is therefore advisable to try diets low in salt for the routine treatment of hypertension with the expectation that a majority of patients will not respond. When renal

* Term suggested by Dr. Willard M. Allen.

function is reduced, this should be done under conditions in which the patient can be carefully watched and plasma chloride levels followed. If the response is good, the diet can be continued; if not, stopped. The rigors of the so-called rice diet are hardly justified considering that similar results can probably be obtained by rigid restriction of sodium chloride alone.

The diets used should contain as little salt as possible, depending upon the response of the patient. One Gm. of sodium chloride may be too much in some individuals. Approximately 0.5 Gm. is about as low as can be maintained under the best conditions. Both of these diets require careful selection of foods and fluids and are usually difficult to maintain when patients are ambulatory. It is hoped that methods other than dietary ones for controlling blood pressure will make this difficult and unpredictable form of therapy obsolete for the majority of patients exhibiting so-called "essential" hypertension.

SUMMARY

The dietary management of arterial hypertension by the use of diets poor in sodium chloride is discussed. The possible rôle of the adrenal cortex in arterial hypertension and its relation to disturbances in salt balance is considered in the light of experimental and clinical evidence. While many subjects do respond favorably to rigid restriction of salt by lowering of blood pressure, psychotherapeutic influences may play a large part in this change in some. If subjects are adequately controlled, the change to be expected is not great and may be absent in patients with severe hypertension in whom therapy is most needed. It is possible that patients who do respond favorably to this diet exhibit a different type of hypertension in which the adrenal cortex is overactive. The mechanism of the response is not understood. No special advantage has been demonstrated in the use of a diet exclusively composed of rice, fruit juices and vitamins, as compared with a normal diet with a similar content of salt, and there are several disadvantages to it.

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# Clinic on Psychosomatic Problems

## Impulsive Behavior in a Crippled Boy*

THE clinics are designed to bring out psychosomatic relationships both in symptomatology of the patient and in the organization of the hospital. Reports are directed by Drs. Stanley Cobb and Allan M. Butler and are edited by Dr. Henry H. W. Miles. This is a report of a staff meeting of the Psychiatric Service of the Massachusetts General Hospital, in which the Orthopedic Service cooperated.

DR. HENRY H. W. MILES: J. T. (No. 462356), a seventeen and one-half year old boy, was referred to the Psychiatric Service from Orthopedics because of his despair over his left thigh, resentment toward the world in general and violent outbursts of physical aggression. He had had osteomyelitis of the left femur for nearly three years, with various complications, culminating in a pathologic fracture. Following this, he had worn a succession of spicas for nine months, then had the misfortune of refracturing the femur just when his progress appeared to be encouraging. It was at this point that he was first seen by a psychiatrist.

The patient's past medical history was noteworthy. At about four and one-half years of age he was hit by a car and bumped his head. The extent of this injury was not known, but the patient believed he was kept in bed by the doctor for two weeks. His left femur was fractured when he was five. At six he had a tonsillectomy. He developed septicemia at the age of nine and was hospitalized for a year. At eleven his left elbow was fractured. When the patient was fifteen, an abscess developed on the left thigh which was incised and drained. This was followed by osteomyelitis for which there have been eight hospital admissions and a number of operations. On four occasions he had had ether anesthesia, each time with severe anxiety.

The boy's parents were both high school graduates of English extraction. The patient had been told that they were never really married and this worried him. His birth and early development were said to have been normal and there were no childhood neurotic traits except temper tantrums. When he was eighteen months old, his parents separated, ostensibly because of the father's alcoholism and infidelity. The patient was sent to his grandmother, then back to his father who had remarried. His stepmother had two children of her own and rejected the patient so he was finally placed in an orphanage when he was six. There he remained for five years, learning that fighting and stealing were the best ways to achieve prestige. When he was eleven, he went back to his mother, who also had remarried and had a two year old son by the second husband. The patient liked his stepfather, a rather friendly, out going man, but soon showed jealousy of his half brother. Outbursts of aggression appeared, once to the point of attempting to choke the little boy.

The patient said that at school he deliberately provoked the teachers and gained a reputation of being a "tough guy." He hoped to be expelled and probably would have been except for the intervention of osteomyelitis. This started when he was in the eighth grade and he never went back to school. About sexual matters he had always been shy. At the age of eleven he developed poison ivy on his genitals and endured severe itching and swelling rather than tell his mother or a doctor. A few years later he was quite upset when his mother had an extramarital affair, and it was about this time that he had fears of a man coming into his room at night to kill him. There were occasional nightmares of being shot

* From the Psychiatric Service of the Massachusetts General Hospital, Boston, Mass.

or stabbed by a man. He masturbated occasionally with feelings of guilt but was unable to tell about this in detail.

Since the time he left the orphanage, the patient had tried to be older and tougher than he really was. He took exercises to build himself up, began to swear, smoke cigars and drink. He loved to get into fights and make other boys cry. Since the beginning of the osteomyelitis, he had become more aggressive and he related numerous fantasies of smashing people in the face, shooting, killing and robbing.

Physical examination was normal except for large scars on the left thigh and disuse atrophy. Complete blood count and urinalysis were normal and x-ray of the chest was negative. Basal metabolic rate was −11. X-ray of the left femur showed marked osteoporosis of areas adjoining the fracture, with incomplete bridging of the fracture by new bone formation and a possibility of sequestration. The electroencephalogram was a borderline record.

The patient's general behavior and manner of speech had a veneer of belligerence, beneath which the mood was one of anxiety rather than aggression. Memory and orientation were normal, general information fair, judgment and insight poor.

After the initial study, therapeutic interviews were begun. A number of hours were spent on his hostility and ventilation was encouraged. It seemed that the patient's anger developed frequently in situations in which he believed others thought him inadequate or weak. He poured out a tremendous number of violent fantasies in which he was vengeful or aggressive. His anxieties, however, were always near the surface, and he told how terrified he was of ether because it might kill him or the doctors might trick him and amputate his leg. He talked about his mother and how much he hated her because she did not love him; but he had a strong attachment to her and related how he was so angry with her lover that he threatened to kill him with a knife. The patient would talk repeatedly about a girl who had shown interest in him and how he was attracted to her and at the same time uneasy. Finally he stated that being near girls made him shaky and sweaty so he had to keep them away by his roughness of manner. This led him back to his fears of ether and he related a dream, associated with his first operation, in which he dreamed he was dead. He then told a story of a Japanese war atrocity in which wounded prisoners' testicles were smashed with a hammer. He talked spontaneously and no interpretation was made to him.

When the hip spica was removed for an orthopedic check-up, the patient became tense, restless, profane and at the same time felt very tired, had "empty" feelings in his chest and felt limp. He disrupted ward morale by smashing windows and threatening suicide. He was afraid to go to sleep at night because something might happen to his leg. We then discussed his feelings about girls and he became reticent. His anxiety was demonstrated, however, by another violent outburst during which his behavior was even more impulsive. It was decided that he could no longer be kept on the ward and when he was told he became upset, anxious and threatened to kill himself as soon as he got out. He then said there was something he wanted to tell but was unable to say it. Finally he wrote it out, describing how he thought his mother had purposely made herself sexually attractive to him and how this had made him masturbate. He related fantasies of raping her and of killing his stepfather so he could possess his mother.

### SOCIAL SERVICE REPORT

MISS BEATRICE TALBOT: The patient's mother was a rather immature woman who never took any initiative about her son's plans. She wrote him simple, chatty letters. His stepfather was a happy-go-lucky, wisecracking sort of man. The patient had not seen his own father for ten years. The patient's paternal grandmother was an energetic woman and a strong Christian Scientist. He was appreciative of what she

had tried to do for him, but usually became fresh and insulting in her presence and was bothered by her attempts to force her religion on him.

The patient was so upset whenever he went home that one of my main functions was to try and arrange to have him stay in Boston. He had lived with his paternal grandmother at a nursing home which he hated, and at a boys' nursing home which he had to leave because they could not look after him medically. There was no member of his family who could give him a home.

The patient had several talents: drawing, writing and singing. He had considerable persistence but had difficulty accepting criticism. The State Department of Rehabilitation would arrange for a training program if he were well enough to pursue it. The Goodwill Inn offers a living place for boys with social guidance and an opportunity to work. They would accept this patient.

### PSYCHOLOGIC REPORT

DR. FREDERICK WYATT: The Rorschach test showed an intelligence quotient between 110 and 120, probably higher because neurotic difficulties interfered with his performance. His responses indicated: (1) Breadth and sensitivity of approach; (2) inhibition of the free use of imaginative faculties due to disturbance of self-regard and constriction of mental activities because of frightening preoccupations; (3) use of his mind in a repetitious pattern of conflict; (4) tension states which resulted in violent discharges; (5) he was friendly although antagonistic at times, and he had a frustrated need for love; (6) there was more need for dependency than the patient could accept; (7) he was worried about his body.

*Diagnostic Impression:* Psychoneurosis, violent outbursts, character disturbance.

### PATIENT INTERVIEW

The patient entered the conference room for brief examination and interview. He was a slim, medium-sized boy on crutches. Nothing new was brought out on physical examination. The interview before the group showed a lad with apparent cooperation and ability to speak up in front of a group, but he looked anxious, talked tough, had a hostile intonation and mien although his answers were civil enough. He explained that when he "gets nervous" he impulsively does things he is sorry for and that he does not know why he acts that way. His anxiety over having his leg examined and x-rayed was connected with his fear that the leg would be no good or would have to be amputated. "How could I do a man's work without a leg"?

### DISCUSSION

DR. MARY A. B. BRAZIER: The electroencephalogram was abnormal, with localization in the right occiput. This kind of variation is found in less than 10 per cent of normal people.

DR. STANLEY COBB: Under diagnosis we must consider psychopathic personality and neurosis. About one-half the psychopaths have abnormal electroencephalograms; many of these have a history of head injury. This boy's behavior was that of a psychopathic personality. These people may be classified under three headings: (1) Hereditary psychopathy; (2) those with abnormal electroencephalograms related to head injury and encephalopathy; (3) character neuroses. The inherited ones are "bad eggs," literally speaking, and the prognosis is not good. The second class is allied to epilepsy and is treated with dilantin or benzedrine without much optimism. Treatment of character neurosis is more hopeful. Which was this boy? How should we handle him? It looked as if the administration would be unable to permit us to keep him here.

DR. LEMOYNE WHITE: Last night he escaped from the ward and stood in the hall cursing loudly, saying he was going to break the doors down. He went back to his room at my request, apologized and said he did not know why he got that way. He said he would promise to be good if he could go

back to the open ward. I did not grant his request and he returned to his room laughing hysterically and said: "I don't care, I like it here. I like it here." He asked for liquor, said he would break out and shoot everybody and that he now had the guts to commit suicide. He hurled himself against the window with enough force to break an ordinary screen. It was an impulsive act with all the power he had. He fell to the floor in a heap and burst into tears. He repeated this cycle at intervals until 12:45 A.M. when I told him firmly that if he continued such behavior he would have to leave.

DR. BERNARD BANDLER: The abnormal brain waves and impulsive behavior suggest postencephalitic behavior. His heredity was bad; one could label both parents as psychopaths. He was suspicious of everyone. The clinical picture was disturbing. There was a real danger that he might kill himself or someone else if handled badly. He had not shown this extreme behavior in the past and I wonder what had mobilized it. He had been encouraged to express his aggressive feelings and he was already terrified of losing control of them. Perhaps pushing him to talk about these feelings and about sex had mobilized his anxiety. The purpose of bringing him here was to allow him to have a relationship which would be safe. He got angry when he felt weak; for example, when people gave him a seat on the subway. He wanted to be a "big shot"; he smoked cigars and drank as a defense against being crippled. He could do something constructive in occupational therapy and have exercise that would develop power in his hands and shoulders. The most important current situation was the orthopedic one and I would let him express his anxiety about it.

DR. COBB: If you want a dynamic explanation, we could say we never saw anyone who was more rejected. He actually believed his mother and father wanted him put out of the way, wanted him killed. In reverse he said he would like to kill them. That is enough to give a normal person a severe neurosis with great inferiority feelings. In addition he had fears about his manhood and about his erotic attachment to his mother. It was a complex neurotic situation plus whatever encephalopathy existed.

DR. HERBERT BARRY: Dr. Bradley helped problem children with amphetamine sulfate. This patient was a little old, but it might be worth trying to see if it would make him comfortable enough to work with him. Also I believe it would be wise to separate disciplinary authority from the doctor who does the interviewing. I would now try to make interpretations on the basis that if you want to get material, you probe and bring up anxiety; if you want to relieve anxiety, you make interpretations.

DR. COBB: His fear of losing his leg was very important. It meant to him that he could not be a man.

DR. ELSE NEUSTADT: This patient had a good intellectual endowment which had never been developed. Could something be done with that?

MISS THEODORA KALEM: He had done some fiction writing and he had some talent for drawing.

DR. EDUARD HITSCHMANN: He found no love in his family, always hate. He was castrated in many ways. If he found an occupation, a job, his character would improve.

DR. COBB: One might consider a pneumoencephalogram to see if he had any cerebral atrophy. I would be against it because the boy would resent the procedure and because the findings would not affect our therapy. The head injury was thirteen years ago. The abnormal electroencephalogram might be due to heredity or to an old head injury; there is one chance in ten that such an electroencephalogram could occur in a normal person. We are therefore probably dealing with a boy who has poor heredity and perhaps an injured brain. We could call him a psychopath and make no effort to treat him. But there is a large anxiety element. From the therapeutic standpoint he has assets. He is likeable, likes to work

and has ability. In psychoanalytic terms, his neurosis is due to rejection, castration and to an Oedipus situation. He has produced evidence that he is not wanted at home, that he fears he will lose his manhood and that he has an erotic attachment to his mother. These problems must be talked out with him further. Also his anxiety must be eased by explaining his behavior to him and by giving him some satisfactory occupation. This can be done by discharging him to a living situation in which he will have satisfying work and by having Dr. Miles continue to see him in psychiatric interviews. The prognosis is uncertain because of the precarious social situation, but with the boy's good assets therapy is well worth trying. Beside the work and interviews he should have a trial of dextro-amphetamine sulfate, 10 mg., at breakfast and noon.

FOLLOW-UP NOTE

During the eight months since discharge from the hospital the patient has been seen about twenty times for psychotherapeutic interviews. He left the hospital with his father who had somewhat reluctantly agreed to assume responsibility for the boy rather than see him committed to a state hospital. This was the first time the patient had seen his father since early childhood and he was at first pleased with the arrangement. It soon became evident, however, that the patient's explosive outbursts and irritability were causing serious friction with the stepmother and her six children. Several interviews were concerned with current material and the patient was allowed to ventilate his feelings. He spontaneously brought up sexual topics, but on the one occasion on which deeper probing was attempted he suddenly developed severe headache and dizziness. This was interpreted to him as his reaction to the anxiety-producing topic and reassurance was given.

The situation at home grew worse and he came to Boston to live with his grandmother. More interviews were possible and the orthopedist discussed open reduction. The patient was made anxious and sleepless by this. Also his stepmother wrote that he could not return to them because she was pregnant. During the next month interviews were frequent and a great deal of reassurance was given. Anxiety over sexual thoughts and fantasies was prominent, and from the material it was possible to point out to him how his aggressive outbursts were frequently related to his feelings of sexual inadequacy. He was encouraged to talk about the operation. In spite of the hateful ideas expressed in interviews his behavior was good. After repeated orthopedic examinations it was decided not to operate and the patient was told to walk with a cane. His mood improved dramatically, and he found a job as an apprentice die cutter.

The patient's first job lasted only two weeks when, through an unavoidable circumstance, he was transferred to a jeweler's shop as an apprentice. After a night of drinking he impulsively stole a wrist watch and pawned it to get more liquor. He was arrested promptly and was frightened to discover that the watch was worth $500.

After the case was investigated the patient was released on a year's probation. He was very discouraged, thought that "the cops would be watching him all the time" and again began drinking and making threats of violence.

When last seen, about four weeks later, he seemed better. He had rented a small apartment for himself, a friend and his grandmother and was planning to paint and decorate it. The prospect of another job was encouraging and the destructive and violent fantasies were less.

CONCLUSION

This case of severe personality disturbance in a crippled, adolescent boy might be diagnosed variously by different psychiatrists. The diagnosis of psychopathic personality carries with it an implication of therapeutic hopelessness, and therefore it was thought preferable to regard the

illness as a neurosis. The interview material allowed a dynamic explanation of the symptoms in terms of early parental rejection which aroused tremendous hostility and insecurity, typical mutilation anxiety and unresolved erotic attachment to his mother. On this basis the outlook was considered more hopeful.

A probing type of psychotherapy mobilized anxiety and the patient began "acting out" his neurotic conflicts in an impulsive manner. It was then decided that further treatment should be of a supportive nature. The therapist allowed the patient to ventilate current problems, but avoided anxiety-laden topics, and reassured him freely. The patient was encouraged to stick at his job as a further means of bolstering his self-esteem. These measures were intended to reinforce, if possible, the patient's repressive mechanisms. Interest was shown in his painting and short stories, through which he expressed many aggressive fantasies.

It was believed that marked improvement could scarcely be hoped for; but if this boy could be prevented from becoming an alcoholic or a criminal, the efforts at therapy will have been well spent.

# Clinico-pathologic Conference

## Hemoglobinuria and Cardiovascular-Renal Disease*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D., of weekly clinicopathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, W. C., (B. H. History No. 139562), a fifty-six year old white, married carpenter, entered the Barnes Hospital for the first time on September 19, 1946, complaining of weakness and jaundice. The family history was irrelevant. In regard to the past history the patient had been told that when he was two years old he had had rheumatism but he stated that he had enjoyed excellent health until two years before admission; at that time he had an episode of "pleurisy" from which he recovered without event. Systemic review was non-contributory. The patient had spent most of his adult life working as a farmer or a carpenter and his habits were good.

About twenty-one months prior to entry he developed sudden pain in the calf of his left leg. The pain was so severe that he was forced to walk with the aid of crutches for several days. He denied any parasthesias or weakness and had not noted either redness or swelling of the extremity but the pain was made worse by motion. The pain spread to involve the muscles of the thigh and the patient became almost totally incapacitated. He was seen by a physician who made a diagnosis of pernicious anemia and gave him injections of liver twice weekly. The patient stated that at the time of this illness his urine had a reddish-brown color. After about six weeks the pain in the leg disappeared and the patient was again able to work until one year before entry when he noted the onset of progressive weakness associated with attacks of dizziness which followed exertion. The symptoms were relieved by rest. This group of symptoms persisted and seven months before his admission he developed difficulty in taking fluids; he noted that they would spill out of the right corner of his mouth. No other neurologic manifestations occurred but his physician told him at the time that he had had a "slight stroke." At the same time the physician noted a yellow color to the patient's skin which had persisted from then on. His urine became still darker; its color, which was described as "wine or dark brown," was attributed by the patient to the taking of a new medication called "Ventrax."

Two or three months prior to entry the patient passed tarry stools for a short period but had no other digestive symptoms. His weakness continued to increase so that even a short walk served to tire him excessively. One month before admission the patient had an episode of sudden complete deafness which lasted only one and one-half hours. Gradually hearing returned and was maintained. Following this episode he sought admission to the Barnes Hospital. In the ten months prior to hospitalization he had lost 30 pounds.

Physical examination at the time of entry revealed the patient's temperature to be 37.6°C., pulse 92, respirations 18 and blood pressure 190/100. He was a well developed,

* From the Departments of Internal Medicine and Pathology, Washington University School of Medicine and the Barnes Hospital, St. Louis, Mo.

well nourished male in no acute distress but he appeared chronically ill. Jaundice of the skin and sclerae was easily seen. The pupils reacted well to light and accommodation. Examination of the fundi revealed tortuosity of the arterioles but no hemorrhages or exudates. The ears appeared normal to examination. The tongue was not atrophied nor was it abnormally red in color. The teeth were in poor condition. The tonsils were large and cryptic. Examination of the lungs revealed them to be clear to percussion and auscultation. The heart was enlarged 12 cm. to the left of the mid-sternal line in the fifth interspace; the rhythm was regular. At the apex a soft blowing grade II systolic murmur was audible and at the left border of the sternum in the fourth interspace a grade II, high-pitched, early blowing diastolic murmur was heard. Examination of the abdomen revealed that the liver edge was palpable 4 cm. below the right costal margin and was sharp and firm to touch. The tip of the spleen was hard and descended 1 to 2 cm. below the left costal margin. On rectal examination the prostate was not enlarged and no other masses were felt. The neurologic examination was within normal limits.

The laboratory data were as follows: Blood count: red cells, 1,930,000; hemoglobin, 6.5 Gm.; white cells, 6,750; differential count: juvenile forms, 1 per cent; stab forms, 13 per cent; segmented forms, 68 per cent; lymphocytes, 16 per cent; monocytes, 2 per cent; reticulocytes, 11 per cent. Fragility test: normal. Urinalysis: albumin, 4+; Bence-Jones protein, negative; benzidine test, 4+; hemosiderin, present; sediment, many granular casts; no red cells. Stool: guaiac negative. Blood Kahn test: negative. Blood chemistry: non-protein nitrogen, 25 mg. per cent; total protein, 7.3 Gm. per cent; albumin, 4.5 Gm. per cent; globulin, 2.8 Gm. per cent; alkaline phosphatase, 1 Bodansky unit. Icterus index: 80. Cephalin-cholesterol flocculation test: negative. Bromsulfalein dye retention: no dye retained in thirty minutes. van den Bergh test: direct, 9.7 mg. per cent (fifteen-minute reading); indirect, 2.1 mg. per cent. Venous pressure: 110 mm. NaCl. Circulation time (decholin): 14 seconds. Electrocardiogram: depression of S-T 1 and 2; T waves: low upright in lead I, diphasic in lead II, inverted in lead $CF_4$; slight slurring of all complexes. Special hematologic studies: sternal bone marrow, hypercellular with 588 normoblasts and 83 erythroblasts per 100 white blood cells. Acid hemolysis test: control cells plus patient's serum, no hemolysis; control cells plus patient's acidified serum, no hemolysis; control cells plus control acidified serum, no hemolysis; patient's cells plus control serum, no hemolysis; patient's cells plus control acidified serum, hemolysis. Serum methemalbumin: present. X-ray studies: Roentgenogram of the chest: "There are adhesions from old pleurisy at the left costophrenic angle. The heart is within normal limits as is the aorta." Open films of the abdomen: "The spleen is slightly larger than normal. The left kidney shadow appears normal but the right seems small." Intravenous pyelograms: "The right kidney is atrophic and non-functional." Films of the skull: "The changes of hyperostosis frontalis interna are present." Films of the right shoulder and of the left knee: "The only abnormalities are those of hypertrophic osteo-arthropathy."

During his hospital stay the patient was put on an hepatic regimen. He received four blood transfusions and his red blood count rose to 2,500,000. He continued to pass dark urine and it was noted that the urine passed during the night was much darker than that passed during the day; the urine consistently contained hemoglobin. The patient remained jaundiced for about three weeks; subsequent examination of the serum revealed no abnormal pigment. Radioactive iron was administered in order to study absorption and excretion of that element, but soon after its administration the patient insisted on leaving the hospital because he felt well. During his stay his temperature had been slightly elevated, averaging about

37.8°c. He left the hospital on October 4, 1946.

He did well for several weeks but ten days before his second admission he again began to note shortness of breath on moderate exertion and experienced episodes of paroxysmal nocturnal dyspnea; he required two pillows under his head at night. Concomitantly, his urine became dark, weakness increased and anorexia developed. He was re-admitted to the Barnes Hospital on November 19, 1946.

At the time of entry physical examination revealed the temperature to be 38°c., pulse 120, respirations 24 and the blood pressure 210/120. The changes from those recorded on the first admission were as follows: The patient was quite dyspneic and orthopneic. Jaundice was less intense than it had originally been on the first admission. Increased tactile fremitus and dullness to percussion were noted at the bases of both lungs. On auscultation of the heart occasional ventricular premature contractions were heard and a protodiastolic gallop rhythm was audible at the left sternal border in the fifth interspace. The liver edge was felt 8 cm. below the right costal margin and was slightly tender. The spleen extended 3 cm. below the left costal margin.

Laboratory findings on this admission were as follows: Blood count: red cells, 1,920,000; hemoglobin, 8 Gm.; white cells, 6,750; differential count: stab forms, 5 per cent; segmented forms, 74 per cent; lymphocytes, 17 per cent; monocytes, 4 per cent. Platelets, 330,000. Reticulocytes, 20 per cent. Blood indices: mean corpuscular volume, 112 cubic micra; mean corpuscular hemoglobin, 38 gamma gamma; mean corpuscular hemoglobin concentration, 35 per cent. Blood chemistry: nonprotein nitrogen, 38 mg. per cent; total protein, 5.4 Gm. per cent; albumin, 3.3 Gm. per cent; globulin, 2.1 Gm. per cent. Icterus index: 120. Cephalin-cholesterol flocculation test: negative. van den Bergh test: direct, 0.8 mg. per cent; indirect, 2.10 mg. per cent. Blood culture: negative. Venous pressure: 195 mm. of saline. Circulation time (decholin): 26 seconds. Electrocardiogram: as before. Roentgenogram of the chest: "There is a moderate amount of fluid at both bases and marked cardiac enlargement."

Following discharge, the patient took 0.2 mg. of digitoxin daily, rested a good part of each day and felt quite comfortable. About three weeks before his third and final entry to the hospital he developed a cough productive of a small amount of white sputum. Concomitantly, slight swelling of the ankles and marked shortness of breath appeared and once again he had to sleep propped up in bed in order to breath comfortably. These symptoms persisted and two weeks before entry the patient developed sudden severe pain in the left upper quadrant of the abdomen which did not radiate but which was aggravated by deep breathing. Two days later his urine appeared to be "black"; he stated that its color was definitely different from that previously observed and attributed the change to the taking of "black medicine" which his physician had given him. The black color disappeared from the urine when the patient discontinued the medicine. The abdominal pains, however, persisted and were severe enough to necessitate the use of codeine for relief and finally on January 14, 1947, the patient was re-admitted to the Barnes Hospital.

At the time of entry his temperature was 37.8°c., pulse 100, respirations 34 and blood pressure 180/90. Changes from the physical findings on his second admission were as follows: The patient was acutely ill and extremely dyspneic, so much so that he was unable to talk. He apparently suffered severe abdominal pain. The skin was grey in color. The sclerae were slightly icteric and the conjunctivae were markedly pale. Slight venous distention was noted in the neck. Examination of the lungs revealed them to be clear to percussion and auscultation. A blowing systolic murmur was heard at the apex of the heart and was also audible along the left sternal border but no diastolic murmur could be made out. The liver was the same size as noted on the earlier

examination but the spleen was not palpable. It was noted, however, that the patient held his abdomen quite rigidly because of pain and adequate palpation was therefore difficult. Two plus pitting edema of the lower extremities was present. Neurologic examination was within normal limits.

The laboratory studies were as follows: Blood count: red cells, 1,210,000; hemoglobin, 5 Gm.; white blood cells, 14,300; differential count: as before. The red cells were microcytic and there was 3 plus anisocytosis. The platelet count was 700,000. Urinalysis: color, brown; albumin; negative; sugar, negative; sediment, occasional granular cast; bile, negative; benzedine test, 3 plus. Stool: guaiac negative. Blood chemistry: non-protein nitrogen, 62 mg. per cent; total protein, 5.4 Gm. per cent; albumin, 3.3 Gm. per cent; globulin, 2.1 Gm. per cent. Electrocardiogram: as before.

On admission it seemed clear that in addition to the extreme anemia the patient's cardiac insufficiency had likewise progressed to an advanced degree. Immediately following entry he was given 2 units of red cell residue slowly through a venous pressure apparatus and was placed in an oxygen tent. Two-tenths mg. of digitoxin was also given. Because of the abdominal pain a surgical consultant saw the patient. Among the diagnostic suggestions were perforated viscus and penetrating peptic ulcer. Because of the patient's critical condition, no surgical intervention was considered. Following repeated transfusions of red cells residue the red count rose to 3,000,000 and the hemoglobin to 9 Gm. Two days after entry the cephalin cholesterol flocculation test was 3 plus and the icterus index 112. On the third hospital day the patient received another transfusion. Shortly thereafter his temperature rose to 40°C. A few moist râles were noted at both lung bases and there was some dullness at the right base. The patient did not cough however and the white cell count was only 6,300. He was fluoroscoped and patchy infiltration was noted in the right lower lobe. Penicillin therapy was instituted. Urinalysis revealed 3 plus albuminuria but the urine did not exhibit an abnormal color grossly. Abdominal pain and distention were not relieved by sympomatic measures.

One week after admission, the patient's dyspnea had improved sufficiently to allow him to lie flat in bed. The venous pressure had fallen to 120 mm. of saline and a satisfactory diuresis was recorded. Nonetheless, the patient's general condition continued to deteriorate. The non-protein nitrogen rose continually to a final value of 158 mg. per cent, the carbon dioxide combining power fell to 25.9 volumes per cent and the chlorides to 94 mEq. per liter. Respirations were rapid and deep. During the twenty-four-hour period prior to death blood drawn at six-hour intervals showed no gross hemolysis. The patient became irrational, then comatose and a uremic frost appeared on his face. He failed to arouse from his coma and died quietly on January 25, 1947. During the final admission his temperature ranged between 38 and 39°C. until the last few days of life when it gradually fell to normal.

### CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: This case is indeed complicated and presents a number of interesting features. Most interesting, perhaps, is the hematologic problem, and we are fortunate indeed that Dr. Maxwell M. Wintrobe, Professor of Medicine at the University of Utah School of Medicine, is visiting us and will join in our discussion.

The patient appeared to be in good health two years before admission. Following an episode of pain in his lower extremity, he apparently developed anemia, passed dark colored urine and developed jaundice. When he was admitted to this hospital, his urine contained no red cells but the benzidine test was strongly positive and we infer, therefore, that he had hemoglobinuria. I think that before we define the hemoglobinuria further we should inquire into the mechanism by which it develops and I shall ask Dr. Carl Moore to open the discussion.

DR. CARL V. MOORE: Hemoglobinuria is usually associated with intravascular hemolysis. It distinguishes hemolytic anemia due to intravascular hemolysis from the types which are produced by destruction of red blood cells in the spleen. That is, hemoglobinuria indicates that red cell destruction is occurring within the vessels and in all probability the spleen has little to do with the process. The causative factors of increased intravascular hemolysis are numerous. Drugs, syphilis, severe exercise and infections all may cause intravascular hemolysis and hemoglobinuria. Hemoglobinuria does not usually appear until the level of free hemoglobin in the plasma has risen to about 135 mg. per cent.

DR. ALEXANDER: When free hemoglobin appears in the serum and the renal threshold is reached, some of the pigment will pass into the urine. What is the rôle of the kidney in regard to the appearance of hemoglobinuria?

DR. C. V. MOORE: No one really knows, but one group of investigators measured the amount of hemoglobin excreted by the kidneys very carefully and found that when the serum level reaches 250 mg. per cent of hemoglobin or higher the rate of excretion of hemoglobin is about 3 per cent of the theoretical clearance. They suggested that about 3 per cent of the glomeruli permit hemoglobin to pass and that with very low levels of hemoglobin in the urine the tubules can resorb it all. As soon as the level goes above the figure of 100 to 150 mg. per cent the tubular absorption falls behind the filtration rate and free hemoglobin then appears in the urine.

DR. ALEXANDER: This patient died in uremia and we therefore would like to inquire whether the kidney is itself damaged by the process which you have described.

DR. C. V. MOORE: Again, there have been few studies on the particular type of hemoglobinuria with which we are dealing here, if this indeed be paroxysmal nocturnal hemoglobinuria. Urea clearances have been carefully studied in several patients and have been found to be normal despite prolonged continued excretion of hemoglobin.

DR. ALEXANDER: In other words you do not believe that we are justified in attributing the uremia to the hemoglobinuria.

DR. C. V. MOORE: I think that the uremia was more likely due to nephrosclerosis than to hemoglobinuria.

DR. ALEXANDER: This patient had a positive indirect Van den bergh test and was jaundiced. In the conversion of free hemoglobin to bile pigment is there any structural damage to the liver? You will recall that his liver was enlarged.

DR. C. V. MOORE: Whenever there is hemoglobinuria and resulting hemoglobinemia, there may be focal necrosis of the liver. This man certainly might have had that lesion despite the negative cephalin-cholesterol flocculation test.

DR. ALEXANDER: The cephalin-cholesterol test did become positive on the final admission. Let us now consider the various types of hemoglobinuria. Dr. Moore has suggested paroxysmal nocturnal hemoglobinuria. Would you comment on the mechanism by which this disease arises, Dr. Wintrobe.

DR. MAXWELL M. WINTROBE: It is thought that there is an abnormality of the red cells *per se;* there is probably another factor which is suggested by the results of the acid hemolysis test. If that test is an index of what happens *in vivo*, it would seem that changes in the pH of the blood are important in the development of hemolysis. However, the fact that normal cells in the presence of acidified serum from this patient did not hemolyse indicates that changes in pH are not alone responsible and points to an intrinsic defect in the cells themselves. We really know very little about the pathogenesis of paroxysmal nocturnal hemoglobinuria and although it is certainly a definite clinical syndrome we can say little about its mechanism. These cases are rather rare; I believe only about fifty have been described in the literature and opportunity for a careful study is therefore not very often obtained.

DR. ALEXANDER: From what you say I would gather that the more acid the serum becomes the more hemolysis there would appear.

DR. WINTROBE: That is correct.

DR. ALEXANDER: Dr. Futcher, would you comment on pH changes which may occur in the blood?

DR. PALMER H. FUTCHER: It is possible that during sleep there is depression of the regulatory centers concerned with the respiratory adjustment of blood pH. During sleep, therefore, carbon dioxide may accumulate in the body and the blood pH may fall slightly. Such acidosis might precipitate hemolysis of abnormal red cells but I do not recall whether or not such measurements have actually been made.

DR. ALEXANDER: Dr. Moore, do you know whether such changes have been observed?

DR. C. V. MOORE: Dr. Ham made such studies and found that the pH in the serum never fell much below 7.2 at night. He postulated that the changes in the tissues might be greater than those measured in the blood but this concept has never been proven.

DR. WINTROBE: I think another factor to be considered is concerned with possible changes in the spleen. There may be alterations in the sinusoids of the spleen which are not duplicated in other intravascular spaces and which may lead to massive red cell destruction. Such a postulate is suggested by those few instances in which splenectomy is followed by improvement; against such an interpretation is the fact that in most instances splenectomy has been without any benefit whatsoever.

DR. FUTCHER: This patient did not develop hemoglobinuria until the age of fifty-six whereas I believe that in most instances the syndrome appears much earlier. I wonder if he would ever have developed hemoglobinuria had it not been for the acidosis which arose secondary to renal insufficiency.

DR. WINTROBE: Certainly very few cases have been described beyond the age of fifty.

DR. C. V. MOORE: I think that one case has been described in a woman who was fifty-two. If our diagnosis is correct in this instance, I believe it is quite strange that at the time the patient developed his most severe acidosis he did not have hemoglobinuria.

DR. FUTCHER: I agree and can offer no explanation for this confusing point.

DR. WINTROBE: I must say that I have a little doubt as to whether this man truly had paroxysmal nocturnal hemoglobinuria although I cannot make much of a case against the diagnosis except for the patient's age and the fact that absence of leukopenia and thrombocytopenia are unusual. When I read the protocol, it occurred to me that perhaps, for some reason or another, autoagglutinins were produced in this patient's blood which led to his initial symptoms, for example, the pain in his leg which might have been due to a thrombosis, and that the subsequent history actually was one of repeated thromboses in various parts of his body.

DR. ALEXANDER: Is pain in the leg common in paroxysmal hemoglobinuria?

DR. WINTROBE: One may get thrombosis and thus pain in any region of the body.

DR. W. BARRY WOOD, JR.: Dr. Wintrobe, were you considering the possibility that this man had a carcinoma of the pancreas associated with multiple venous thromboses?

DR. WINTROBE: No, I was not thinking of any such specific mechanism. Very occasionally in atypical pneumonia, cold-agglutinins may be produced to such a high titer that hemolytic anemia occurs. However, here we have no story of pulmonary infection of that magnitude.

DR. ALEXANDER: Is there any specific lesion which at autopsy will enable the pathologists to diagnose paroxysmal nocturnal hemoglobinuria?

DR. WINTROBE: There is no specific lesion although hemosiderosis of the kidneys is perhaps the most consistent finding.

DR. C. V. MOORE: Dr. Wintrobe, in regard to your point concerning the absence of leukopenia, all of the white blood cell

counts done were of course not reported in the protocol. On January 17th the patient's white count was 1,600 and the platelet count 133,000. Six days later the white count had fallen to 700

DR. ALEXANDER: Is leukopenia apt to be constant?

DR. WINTROBE: It is usually fairly consistent although occasionally with an acute exacerbation the count may rise.

DR. ALEXANDER: When this patient was first admitted to the Barnes Hospital, a chest x-ray revealed that the heart size was normal and the venous pressure and circulation time likewise were within normal limits. At that same time the electrocardiogram revealed a number of abnormalities and a diastolic murmur was heard along the left sternal border with a systolic murmur at the apex. No signs of cardiac decompensation had appeared. Two months later his heart had increased in size. The venous pressure and circulation time were greater and he complained of paroxysmal nocturnal dyspnea; that is, he developed all the signs of cardiac insufficiency. Dr. Massie, do you have any comment as to why cardiac insufficiency appeared?

DR. EDWARD MASSIE: This patient probably had hypertensive cardiovascular disease and, with the added load of a marked anemia, developed cardiac failure. He did have a history of rheumatism at the age of two years and if one were to consider the findings he might be able to make a fair case for rheumatic heart disease. There were systolic and diastolic murmurs; the latter certainly suggests aortic insufficiency. However, I think it is more likely that the diastolic murmur represented a hemic phenomenon and the hypertension certainly could have given rise to the systolic murmur. In subsequent examinations the diastolic murmur could not be heard and since aortic insufficiency due to rheumatic valvulitis should have at least persisted and probably would have progressed, I believe the evidence favors the interpretation that the aortic diastolic murmur was due to the anemia.

DR. ALEXANDER: Would you expect to find coronary damage?

DR. MASSIE: Very likely. Part of the enlargement may have been due to dilatation which accompanied the increased cardiac insufficiency as well as the effect of persistent severe anemia. It is well to point out, however, that if the patient had some degree of coronary sclerosis the additional burden of a severe anemia might have produced sufficient myocardial anoxemia to have precipitated a myocardial infarction. We are all familiar with patients with pernicious anemia who have angina when their red cell count is very low and are subsequently free of any anginal pain once their blood count returns to normal.

DR. ALEXANDER: This patient had a small kidney on one side and he died in uremia. Dr. Schroeder, would you comment on this aspect of his illness?

DR. HENRY A. SCHROEDER: From the results of the pyelograms it seems that the patient had only one functioning kidney. It occurred to me that if only one kidney was functioning the deposition of hemosiderin in the tubules might be greatly increased and therefore lead to renal damage more quickly than would be the case had the patient had two normal kidneys originally. The development of cardiac failure adversely effects nitrogen retention, and, in a kidney which is on the verge of failure anyway, may lead to definite azotemia. I believe the patient probably had nephrosclerosis, perhaps a great deal more than would have been predicted on the basis of his blood pressure and the size of his heart. His blood pressure may have been lowered because of the anemia.

DR. WOOD: Dr. Schroeder, do you think that this patient had unilateral pyelonephritis leading to hypertension? Why was the right kidney smaller?

DR. SCHROEDER: I cannot answer your question on the basis of the data at hand. Statistics from the Mayo Clinic indicate that hypertension is no more common in patients with organic renal diseases than in the rest of the population. There are, how-

ever, some cases on record in which removal of one diseased kidney has been followed by prolonged improvement in the level of the patient's blood pressure. It is my own belief, from a study of factors contributing to the onset of hypertension, that in predisposed individuals pyelonephritis may initiate and maintain hypertension indistinguishable from the so-called essential type and, furthermore, that this sequence occurs more often than is commonly appreciated.

DR. ALEXANDER: Dr. Kenamore, do you believe that the severe abdominal pain could have been due to a peptic ulcer?

DR. BRUCE D. KENAMORE: I thought that perhaps thrombosis of the splenic vein had given rise to the pain; it may be accompanied by signs of associated peritoneal irritation.

DR. ALEXANDER: Does it not require a rather large clot to thrombose the splenic vein?

DR. WINTROBE: I think it is perhaps more likely that the patient had a splenic infarct with resultant peritoneal irritation.

DR. ALEXANDER: Dr. Schroeder, do you think there will be specific tubular damage due to hemosiderin?

DR. SCHROEDER: I read in Dr. Wintrobe's book that hemosiderin is deposited in the tubules in this disease.

DR. ALEXANDER: Dr. Moore, do you agree that the patient had intravascular thromboses?

DR. C. V. MOORE: I think so, but I still believe that he had paroxysmal nocturnal hemoglobinuria.

DR. WOOD: I am still interested in knowing what lesion will be found in the right kidney. It did not function properly and I believe the pathologists will be able to tell us why.

DR. ALEXANDER: You believe that it probably represents the end result of pyelonephritis, do you not?

DR. WOOD: I think so.

DR. ROBERT J. GLASER: This man had an aortic diastolic murmur on his first admission. I wonder if Dr. Wintrobe would comment on the occurrence of aortic diastolic murmurs in severe anemia. We have not infrequently heard mitral diastolic murmurs under such circumstances but the others have been rather rare in our experience.

DR. WINTROBE: I agree that hemic aortic diastolic murmurs are quite unusual but I think that one must be cautious in commenting about the murmurs which are heard in association with hemolytic anemia. I think all of us have had the experience of listening to the hearts of patients with sickle cell anemia and have been convinced that there were valvular lesions, only to learn subsequently from the pathologists that no valvular defects were present.

DR. GLASER: You would not be surprised if there was no aortic lesion at all?

DR. WINTROBE: I would not.

DR. ALEXANDER: Would you be surprised, Dr. Glaser?

DR. GLASER: No.

DR. SCHROEDER: This patient had hypertension and aortic diastolic murmurs may occur as a result of hypertension.

DR. ALEXANDER: In conclusion, it seems that we agree that this patient had hypertensive cardiovascular disease and arteriolar nephrosclerosis. Myocardial infarction due to the combination of coronary sclerosis and severe anemia has been proposed. The patient likewise certainly had hemoglobinuria, and the evidence seems to favor the diagnosis of paroxysmal nocturnal hemoglobinuria although there are various factors including the patient's age which are somewhat against that diagnosis. A splenic infarct may well have explained his abdominal pain and the possibility of intravascular thromboses has likewise been mentioned.

*Clinical Diagnoses:* Paroxysmal nocturnal hemoglobinuria; hypertensive cardiovascular disease; arteriolar nephrosclerosis; myocardial infarction; infarct of the spleen; intravascular thromboses.

PATHOLOGIC DISCUSSION

DR. FRANK TOWNSEND: At the time of autopsy the principal external finding was

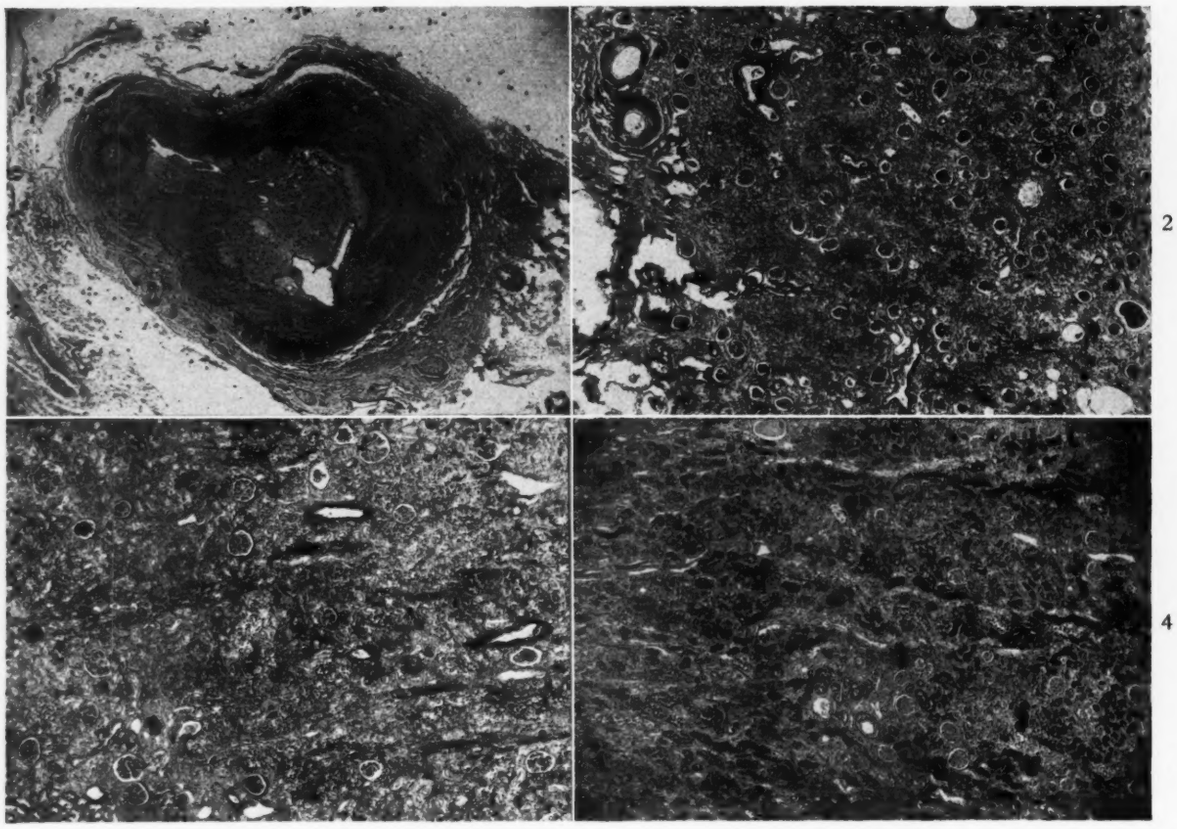


FIG. 1. Section of the right renal artery showing an organized, recanalized thrombus in the lumen.
FIG. 2. Section of the cortex of the right kidney through the atrophic portion. Note the degree of fibrosis and hemosiderosis.
FIG. 3. Section of the cortex of the left kidney. Note that the glomeruli are larger in size and that the degree of fibrosis and atrophy is less than is seen in Figure 2.
FIG. 4. Section of the cortex stained for iron. Note the large amount of hemosiderin in the epithelium of the convoluted tubules and of the ascending loops of Henle.

the yellow color of the skin. On opening the thorax examination of the heart revealed the presence of a fibrinous pericarditis. One hundred thirty-five cc. of serofibrinous fluid were present in the pericardial cavity. The heart was enlarged, weighing 610 Gm. There was moderate sclerosis of the coronary arteries, especially of the anterior descending branch of the left coronary artery, which at one point was practically occluded by an arteriosclerotic plaque. In the septum there was an area of greyish tissue in which depressed, red, irregular foci were seen; it was believed that the changes represented a healing infarct. The only other point of interest in the heart was that there were subendocardial ecchymoses in the right atrium. No valvular abnormalities were present. The aorta was moderately sclerotic.

The lungs weighed 1,970 Gm. The right pleural cavity contained no fluid but in the left cavity 400 cc. of serous fluid were present. Most of the right pleural cavity was obliterated by fibrous adhesions. In the mucosa of the trachea and bronchi, which was yellowish-white in color, there were many small ulcers. The trachea and bronchi were filled with bloody, mucoid material. The periphery of the lungs was firm.

One hundred cc. of serous fluid were present in the peritoneal cavity. The left kidney weighed 316 Gm. and the outstanding feature in the gross was its extremely brown color. On cut surface differentiation of the cortex and medullary portions revealed them to be of normal proportions; in the renal pelvis there was a reddish area 1 cm. diameter. The right kidney weighed

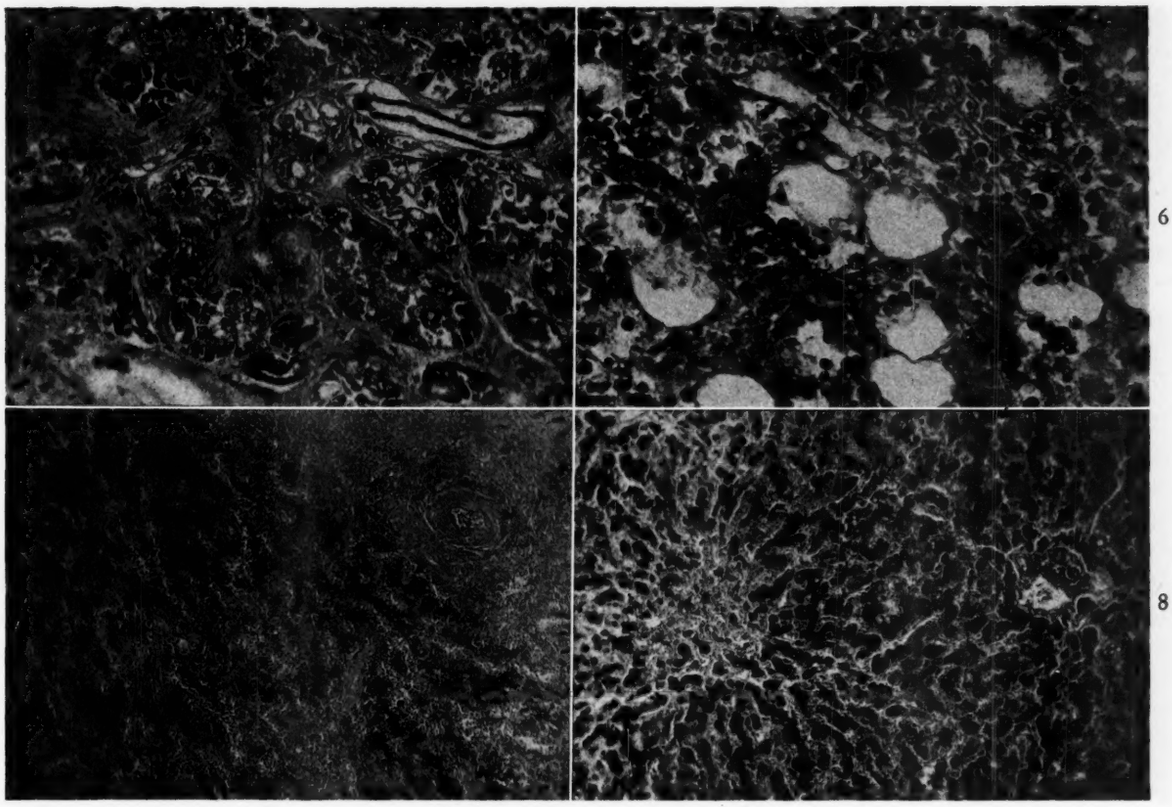


FIG. 5. A higher power view which shows in better detail the changes described in the previous section.
FIG. 6. Section of the femoral marrow showing hyperplasia, particularly of the erythrocytic elements.
FIG. 7. Section of the spleen showing the marked hemosiderosis.
FIG. 8. Section of the liver which shows the changes of chronic passive congestion.

95 Gm. There was an old organized thrombus within the lumen of the main right renal artery which was completely occluded, but an aberrant renal artery, supplying the upper pole of the kidney, was patent. There was a definite line of demarcation between the upper and lower portions of the kidney. The tissue in the upper one-third appeared much as that in the left kidney, whereas the lower two-thirds of the right kidney had lost its characteristic appearance. The pancreas weighed 210 Gm. and appeared edematous. The spleen was enlarged, weighing 240 Gm. On examination the outer surface had depressed areas and on cut surface numerous grey areas were seen; others were red and hemorrhagic in appearance. Between these foci, which were interpreted as infarcts, there were areas of tissue which appeared normal except for their brown color. There were fibrinous and fibrous adhesions between the spleen and the omentum and diaphragm. The liver weighed 2,850 Gm. and the outer surface was not remarkable. On gross examination of the cut surface the only change from the normal was a slight increase in blood. There were superficial erosions of the mucosa in the lower portion of the esophagus. The remainder of the gastrointestinal tract was normal. The bone marrow was red and appeared hemorrhagic.

DR. MARGARET G. SMITH: The first section (Fig. 1) is that of the organized and recanalized thrombus in the right renal artery. Most of the lumen is occluded but the degree of organization and recanalization indicates that the thrombus is quite old. The orifice of the artery was nearly occluded by an arteriosclerotic plaque and it is probable that the thrombus within the vessel arose on that basis. In Figure 2 a section of the cortex of the atrophic part of the right kidney is seen. As Dr. Townsend

has told you approximately two-thirds of this kidney was atrophic. The glomeruli are small and fibrotic, the tubules throughout the cortex are atrophic and there is an increase in the interstitial connective tissue. A large amount of hemosiderin is seen in the atrophic tubules and also in the interstitial connective tissue. Most of the deeply stained areas in the section represent hemosiderin. The next section (Fig. 3) is from the cortex of the left kidney. In comparison with the section from the right kidney the glomeruli are definitely larger. There is some interstitial fibrosis and atrophy of the tubules but much less than was present in the atrophic part of the right kidney. In another section thickening of the walls of the arterioles was seen. In addition there was fibrous thickening of the glomerular capsules and thickening of the basement membranes of the capillaries in the glomerular tufts. Atrophy of the tubules, which is apparent, may be explained on the basis of arteriolosclerosis, but one must consider also the possibility that some of this damage may have been caused by the large accumulation of iron which is seen in the tubular epithelium. Figure 4 shows a section of the cortex stained for iron. There is a great amount of hemosiderin in the epithelium of the convoluted tubules and of the ascending loops of Henle; atrophy of the tubules and interstitial fibrosis may also be seen. In another section a few casts having the staining characteristics of hemoglobin were present. Hemoglobin casts were found in the convoluted tubules of the loops of Henle, and there were some hyaline casts in the distal convoluted tubules. Figure 5 shows the large amount of hemosiderin in the epithelium of the convoluted tubules and the degeneration of the epithelium. There was no necrosis of the renal arterioles such as is seen in malignant hypertension. However, in a section of the pancreas some of the arterioles did show necrosis. There were some foci of necrosis in the pancreatic tissue and, occasionally, fibrin thrombi were seen in the capillaries. There was edema of the connective tissue about the pancreas with deposition of fibrin. These changes in the pancreas may have accounted for some of the patient's pain in the later days of his illness, but it seems more likely that the pathologic changes in the spleen were responsible for the pain which was present for three weeks. A section of the femoral marrow showing hyperplasia is seen in Figure 6; the hyperplasia chiefly involves the erythrocytic elements. The capillaries are dilated and filled with red blood cells. In a section of the spleen (Fig. 7) there is a large amount of hemosiderin within phagocytic cells between the sinusoids; some of the phagocytes contain both red blood cells and granules of hemosiderin. In other sections of the spleen there were organized and recent thrombi in both arteries and veins. Arteriosclerosis was not marked in the splenic arteries and does not offer a satisfactory explanation for the formation of thrombi. In a section of the liver (Fig. 8) there is loss of liver cells at the center of the lobule. The sinusoids are dilated. These changes are interpreted as being those of long standing chronic passive congestion. The Kupfer cells, which cannot be seen distinctly in the section, contain red blood cells and a small amount of hemosiderin.

A section of the anterior descending branch of the left coronary artery revealed almost complete occlusions of the lumen by an arteriosclerotic plaque; the sclerotic changes in the rest of the coronary arteries, as Dr. Townsend stated, were moderate. Sections of the myocardium showed changes characteristic of healing and recent infarcts. In the areas of recent infarction there was necrosis of muscle fibers with absence of nuclei and striations. In the older part of the infarct there were no muscle fibers, only vascular connective tissue having thin collagen fibrils. Because of the vascularity of the connective tissue and the lack of dense collagen fibers, it was thought that that part of the infarct was a few weeks old.

In summary, the major findings included arteriosclerosis of the coronary arteries with healing and recent infarcts of the myocar-

dium. There was occlusion of the right renal artery with atrophy of two-thirds of that kidney. Moderate arteriolar nephrosclerosis was present. It is possible that the occlusion of the renal artery with resulting renal ischemia was of importance in the development of hypertension. The heart was hypertrophied and dilated, and fibrinous pericarditis, a manifestation of uremia, was present. There was much hemosiderin in the epithelium of the convoluted tubules and of the loops of Henle; degenerative changes were present in the epithelium. There were hemoglobin casts in the collecting tubules. Degenerative changes in the renal tubules are not reported in most cases of paroxysmal hemoglobinuria, but it is possible that they occurred in this patient because renal damage due to arteriolosclerosis was also present. Erythrophagocytosis and deposits of hemosiderin in the spleen are likewise not reported in paroxysmal hemoglobinuria, but in this instance can be related to the blood transfusions which the patient received. The abdominal pain may be explained on the basis of peritoneal irritation arising as a result of recent infarcts in the spleen.

*Anatomic Diagnosis:* Arteriosclerosis of the coronary arteries, moderate of the right, advanced of the left; healing and recent infarcts of the interventricular septum; arteriosclerosis of the thoracic and abdominal aorta, moderate, with plaque narrowing orifice of right renal artery, of the splenic artery, moderate; organized thrombus in the right renal artery; aberrant artery to superior pole of right kidney; atrophy of the inferior two-thirds of right kidney; arteriolar nephrosclerosis, moderate; hypertrophy and dilatation of the heart (610 Gm.); chronic passive congestion of the liver; hydrothorax, left (400 cc.); serofibrinous pericarditis (150 cc.); necrosis of arterioles and small arteries in pancreas; fibrin thrombi in capillaries in pancreas; foci of necrosis of pancreas; acute necrotizing bronchitis and tracheitis; hemosiderosis of the kidneys, advanced; congestion and focal hemorrhage of the bone marrow; organized and recent thrombi in veins and arteries in the spleen; healing and recent infarcts in the spleen; hemosiderosis of spleen, moderate; splenomegaly (440 Gm.); erythrophagocytosis in liver, spleen, bone marrow and lymph nodes (history of blood transfusions).

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# Case Reports

## Traumatic Rupture of the Aortic Valve*

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A REVIEW of the literature up to the year 1928 by Howard[1] revealed 113 cases of ruptured aortic valve as the result of muscular effort or trauma and that Plenderleath[2] reported the first case in 1830. There were fourteen of these cases proven by autopsy to be due to contusion and a search of the literature up to the present time has failed to reveal any additional cases. The first of the two cases discussed here was previously reported[3] but is reviewed for comparison with the second case.

### CASE REPORTS

CASE I. K. S., a single white male, aged twenty-two years, with a normal family and past history was injured in an explosion which completely buried him by stone and débris. There were numerous fractures and lacerations of the entire body including a fracture of the sternum with discoloration of the entire anterior and posterior surface of the thorax due to contusions. When he regained consciousness he complained of a crushing sensation in his left chest associated with severe dyspnea. After eight months he had recovered from the external injuries but during this time he continued to complain of the crushing sensation in the left chest, of moderate dyspnea which became severe on exertion, of moderate palpitation on exertion, frequent attacks of syncope, severe dizziness and anxiety with fear of impending death. During the attacks of severe dizziness and syncope he would first become pale followed by cyanosis of the lips and fingernails. Fourteen months after the accident he had pain in the right kidney region and signs of congestive heart failure which caused his death two days later. An examination a year before the accident revealed this man to be normal in every respect. Another examination two days before death showed engorgement of the neck veins, swinging of the carotid arteries and a pulsation in the suprasternal notch. The apex beat was not palpable and the cardiac dullness in the fifth interspace was 10 cm. to the left and in the fourth interspace 5 cm. to the right of the mid-sternal line. There was a loud, rough, diastolic murmur heard at the base of the heart and along the left border of the sternum, with the maximum intensity at the aortic area. There was also a slight roughness of the first sound at the apex. The rhythm of the heart was regular and the rate was 96. The pulse was of the Corrigan type with a 110 mm. systolic and 20 mm. diastolic blood pressure. The liver was at the costal margin but there were many moist râles in the bases of both lungs. The urine contained a large amount of albumin, no sugar but many red blood and pus cells. The blood count was 80 per cent hemoglobin, red blood count 4,320,000 and the white blood count 15,200. The orthodiagram showed a transverse diameter of the heart of 15.5 cm. The Wassermann reaction was negative. The diagnosis was traumatic heart disease, ruptured aortic valve, aortic insufficiency, myocardial insufficiency and congestive heart failure with possible embolism of the right kidney.

Autopsy results were as follows: The sternum was separated at the synchondrosis sternalis between the manubrium and the body of the sternum in such a manner that it was easily hinged outward and the periosteal fibers supporting this synchondrosis were relaxed so that the body of the sternum was easily displaced backward into the mediastinum to the extent that it overrode the lower margin of the manubrium sterni. The myocardium of the left ventricle was of the usual thickness and of good consistency. The cusps of the aortic valve were

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ragged and partially covered with precipitated blood. There was a transverse slit just below the margin of the left posterior cusp, the right posterior cusp was irregularly torn, fragmented and infiltrated with blood and the anterior cusp was also extensively torn. There was no gross evidence of any inflammatory reaction. The valve was entirely incompetent. At the base of the anterior cusp the adjacent myocardium and the subpericardial adipose tissue was discolored a dark, reddish brown by an old hemorrhagic infiltration. The remainder of the heart was normal. The lungs contained a moderate amount of edematous fluid and diffuse congestion. There was a large area of infarction in the right kidney.

Microscopic sections of the ruptured cusps of the aortic valve showed a thin fibrous structure and on both surfaces of the valve a precipitate of hemorrhagic material. Immediately adjacent to the fibrous tissue of the valve was a thin layer of plasma cells and a small amount of fibrin while external to this, red blood cells were arranged in a granular material simulating the precipitation type of blood clot. The sections through the myocardium and subpericardial tissue at the base of the aortic valve showed infiltration with round cell and non-nucleated cells and throughout the entire section there was an extensive deposition of blood pigment. Other sections of the myocardium were normal. In the lungs the alveolar spaces were filled with edematous fluid in which there were a few red blood cells and many heart failure cells. The sections of the right kidney through the area of infarction showed a complete destruction of the kidney tissue and replacement with a hyalinized homogeneous material.

*Diagnosis:* Rupture of the aortic valve, hemorrhagic infiltration about the base of the aortic valve, separation and dislocation of the sternal synchondrosis, bilateral congestion, edema of the lungs and infarction of the right kidney.

Case II. L. B., a married white male carpenter, age fifty-eight, with an irrelevant history except for influenza in 1918 and a herniotomy in 1931, was injured in May, 1937. While running, he had jumped over a concrete form and a lath flew between his legs which threw him to the soft muddy ground in such a manner that he struck his chest and abdomen with his arms extended. He immediately arose and walked to his automobile when he felt and heard a thrill or purring in his upper chest and noticed soreness in the sternal region. As he drove home he continued to hear this peculiar sound and developed some palpitation, tachycardia and slight dyspnea. That evening his wife was alarmed when she heard this purring-like noise at a distance of three feet from the patient. An examination revealed engorgement of the neck veins with swinging carotid arteries. The apex beat was in the fifth interspace 7.5 cm. to the left of the mid-sternal line and there was a pronounced thrill felt over the midsternum and in the aortic area. The cardiac dullness in the fifth interspace was 8 cm. third interspace 4.5 cm. to the left and in the fourth interspace 4.5 cm. to the right of the mid-sternal line. A loud, rough, musical diastolic murmur was heard at the aortic area. This murmur together with a soft systolic murmur was also heard at the mitral area. The rhythm was regular with an occasional premature contraction, the pulse rate was 72, Corrigan in character, and there was a definite capillary pulsation. The liver was at the costal margin and tender, the blood pressure was 130 mm. systolic with a diastolic of 0 mm., the blood Wassermann reaction was 4 plus; Kolmer's test was 3 plus, Kahn's test showed 4 plus and a non-protein nitrogen count was 44 mg. Under the orthodiagram the heart was normal in size and contour and in the second oblique position there was a slightly abnormal pulsation of the first part of the aorta. The electrocardiogram was normal with left axis deviation, the vital capacity was 72 per cent and the venous pressure was 40 mm. of water. A diagnosis was made of traumatic heart disease with traumatic rupture of the aortic valve and aortic insufficiency. This man continued to work with no marked changes except a slight increase in dyspnea and some decrease in vital capacity, until four months later when the transverse diameter of the heart under the orthodiagram was observed as 15 cm. After nine months he had severe substernal pain referred through to the left scapula followed by a marked cough, severe dyspnea and orthopnea which required oxygen and a narcotic for relief. One month later the transverse diameter of the heart was 17.2 cm. and the electrocardiogram showed a depression of the RST segment in lead 1 with a low take-off and a negative T wave, a slightly negative T2 and an upright T3 with slightly elevated RST segment, in addition to an increased left axis deviation. The blood pressure at this time was 180 mm. systolic, 0 mm. diastolic and the heart rhythm was regular with a

rate of 100. He had severe chest pains every two to three days which would sometimes last for forty-eight hours and he developed definite attacks of paroxysmal nocturnal dyspnea. After eighteen months the transverse diameter of the heart was 18.4 cm. and the blood pressure was 220 mm. systolic, 0 mm. diastolic. The pain and nocturnal dyspnea were even more severe with occasional signs of pulmonary edema and slight edema of the ankles. These symptoms were benefited somewhat by the use of oxygen especially during the night. A month later he had an acute attack of pulmonary edema with marked congestive heart failure; however, he improved under treatment but it was necessary now to give a mercurial diuretic every two or three days to prevent the advance of congestive heart failure. From twenty-two months on the patient was almost continuously in congestive heart failure and required a narcotic every few hours for relief from the terrific pain in his chest. Then, after twenty-seven months incisions were made on the lateral surfaces of both legs just above the ankles in order to drain the edema fluid which could not be controlled by the mercurial diuretics. This gave him some relief for a short time and reduced the edema and ascites but shortly after this he died, just two years and three months after the injury.

Autopsy findings were as follows: The general description of the body was an emaciated, white man sixty years of age with a small surgical incision on either side of both ankles. The thorax was opened revealing an enormously enlarged cardiac area which measured 19 cm. in the widest transverse diameter. The right border extended approximately 1 cm. beyond the right sternal margin while the apex was against the left thoracic wall. The left lung was confined above the enlarged heart and the right lung was completely bound down by adhesions. The pericardial sac contained the usual amount of clear, amber fluid. The enormously enlarged heart measured 18.5 cm. in the widest transverse diameter and the right auricle was engorged with blood. The pulmonary and tricuspid valves were normal but slightly widened. The aorta was smooth and pliable, except for an occasional area of atherosclerosis. The aortic valve presented an unusual picture in that there was a splitting and separation of the commissures between the right and left posterior cusps resulting in a sagging, free, flap-like part of these cusps, which moved with equal ease either upward into the aorta or downward into the left ventricle and produced a definite, permanent opening along the line of the separated commissures. The anterior cusp was normal. The two cusps of the valve which were involved by this separation of the commissures were unusually smooth, fibrous in character with an average of 1 or 2 mm. in thickness. The mitral valve was normal and the myocardium of both right and left ventricles was extremely hypertrophied. In the left lung there was a small amount of congestion and edema and the right lung, which was firmly adherent to the chest wall, diaphragm and mediastinum, showed an encapsulated empyema between the lower lobe and diaphragm, with approximately 4 ounces of thin, greenish, foul-smelling pus and also an adjacent abscess which measured 4 cm. in diameter. The remainder of the lung was moderately congested but not consolidated. The liver was 4 cm. below the right costal margin, dark in color, and moderately congested. All other structures and organs were normal.

Microscopic sections showed an acute bronchitis in the lungs, partial atelectasis, some edema, numerous heart failure cells, advanced pulmonary arteriosclerosis and in the lower lobe of the right lung a dense replacement fibrosis of the pleura, passing through a zone of granulation tissue into a purulent exudate lining the encapsulated empyema. In the sections of the myocardium from both ventricles there was marked hypertrophy of the individual cells with an occasional area of granular degeneration. Sections through the traumatic commissure of the aortic valve showed hypertrophy of the myocardium at the base of the valve with the myocardial cells and their nuclei quite large. The blood vessels within the myocardium at this point were somewhat thickened. Immediately adjacent to the commissure there was some granular degeneration of the myocardial cells and the commissure itself showed an acellular fibrosis with a few round cells distributed through the fibrous tissue. The surface was covered with a thin layer of endothelium. The myocardium from other portions of the left ventricle was extensively hypertrophied with occasional small areas of brown atrophy. The aorta above the valve had an intact surface and intima but the adventitia showed a few round cell accumulations which extended into the media. The vaso vasora, however, were normal and the round cell infiltration was not associated with these blood vessels but appeared diffusely in the medial and advential layers. Also within

the media there were areas of hyalinized fibrosis and limited areas of degeneration and calcification. The injured leaflets of the aortic valve were partly covered with endothelium and the entire valve was thickened with an acellular connective tissue which was completely avascular. There was no evidence of recent or old hemorrhage, except in very occasional areas at the base of the valve where there were a few granulation type capillaries, about which there were a few monocytic and round cells and a small amount of pigment.

*Diagnosis:* A partly healed traumatic rupture and separation of the commissures between the posterior cusps of the aortic valve, progressive fibrosis and relaxation of the cusps of the aortic valve, permanent aortic insufficiency, myocardial hypertrophy and granular degeneration, chronically suppurative empyema and lung abscess of the right lung, acute bronchitis, edema, heart failure cells, partial atelectasis, advanced pulmonary sclerosis of the lungs and congestion of the liver.

## COMMENTS

Of the 113 cases reported by Howard there were only fourteen proven cases of patients with no evidence of syphilis and in only thirteen out of forty-eight autopsies of the entire series was the aortic valve reported absolutely normal. This was true, however, in 44 per cent of patients in the traumatic group as against only 23 per cent of those in the strain group. In the second case reported here, while there was some syphilitic aortitis, there was no evidence at autopsy of syphilitic involvement of the aortic valve which could weaken the cusps causing spontaneous rupture. It was previously thought that the traumatic lesion was the result of a fall from a height and did not occur following such trauma as burial under an avalanche of débris. However, case 1 and others have lately demonstrated the fallaciousness of the view that rupture could be due only to bursting and that the gradual pressure applied by burying was not sufficient to cause this lesion. Bernstein[4] made the interesting observation that tears of the aortic valve cusps are only partial because as soon as the rupture occurs the pressure is relieved, preventing further tearing. External injury such as falling against the anterior chest wall or burial under débris causes the column of blood in the aorta during cardiac diastole to increase suddenly to the degree that the wall of the aorta or cusps of the closed aortic valve tear. The older writers believed that this type of rupture usually occurred in only one cusp; however, in both of the cases presented more than one cusp was injured.

Traumatic valvular rupture occurs in both normal and diseased valves but great care should be taken in differentiating the latter from spontaneous rupture, which most frequently occurs without any injury or muscular activity and is more frequently confused with injury produced by overexertion. The aortic valve is most frequently injured by contusion. The tears of the cusps heal with the formation of scar tissue, especially when the tear is along the base or commissure of the leaflet. Besides fragmentation of the free edge of the cusp, rupture of the chordae tendineae and papillary muscles also occurs. These injuries, when the result of contusion, are usually associated with other traumatic lesions. Healing of the fragmented parts of the valve cusps results in thickening which tends to smooth off the rough edges. The thickening thus caused produces stenosis and a certain degree of insufficiency. Frequently the fragments will grow together or become attached to the wall of the ventricle but it appears that complete healing with obliteration of the entire opening does not occur.

The absence of immediate severe symptoms following injury or exertion is strong evidence of a spontaneous rupture rather than a traumatic tear. The most characteristic and immediate symptom in the latter condition is acute and frequently agonizing chest pain of a sharp, tearing character located substernally and across the upper chest. This pain radiates up to the neck and down the left arm or through to the back between the shoulder blades, and may be accompanied by anguor animi

or sense of impending death such as is associated with angina pectoris and coronary artery occlusion. Severe dizziness, vertigo with faintness and syncope are early symptoms. There is also an early development of rather severe dyspnea and palpitation with a sensation of roaring and pulsation in the chest, neck and ears. The murmur frequently can be heard not only by the patient but by others at quite a distance. This peculiar phenomenon has been described by various patients as "the cooing of a dove";[5,6] "rumbling, rustling noise";[7] "a humming noise";[8] "the croaking of a frog";[9] "a whistling noise";[10] "a buzzing in the chest";[11,12] "musical murmur or thrill";[13,1] "rattle in the head";[14] "whirring noise";[15] or a "purring." Of course, all the classic signs and symptoms of aortic insufficiency also develop immediately.

Associated with a diastolic murmur, loudest at the base of the heart, is a systolic murmur. The hypothesis of Foster[16] is that this is due to vibrations of the valve cusps floating in the blood stream. He adds that if this is true, the systolic murmur has a certain prognostic importance and also that when the murmur spreads towards the apex it is due to insufficiency of the left aortic segment; if it spreads toward the ensiform cartilage, it is due to insufficiency from a lesion of the right and posterior cusps. He describes the diastolic murmur as of a special blowing and flapping character. According to Strassman[17] it is often longer, of a peculiar tone and more intensive than the soft murmur of aortic regurgitation due to endocarditis. In the review by Howard[1] the murmur was described as, "harsh or intense," in nine cases, "prolonged and loud, gushing, rumbling, creaking, flapping, rough and flapping, rasping or piping," each in one case. In six cases it was described as musical, without other qualification, while in nine other cases the musical quality was modified by such terms as "sibilant" in two cases, "vibrating, tone like the vibration of a string, piping, buzzing, purring, like a torn sail" and "siren-like" each in one case. The marked thrill frequently associated with this murmur, it should be remembered, is caused also by traumatic rupture of the septum. Frequently total disability occurred almost immediately but in a few instances light work could be continued for a short time. The disability was probably due to sudden regurgitation of blood into the left ventricle before adequate compensatory hypertrophy could take place. The two cases of traumatic rupture of the aortic valve described in this report did not show acute dilatation but steady progressive enlargement of the left ventricle. The definite healing tendency of rupture of the aortic valve accounts for the favorable short-term prognosis; but the resulting aortic insufficiency progresses in the usual manner and at a much more rapid rate than when caused by disease, with the same ultimately fatal result. Barie[18] believed that perhaps the prognosis was more grave when the rupture interfered with maintaining diastolic blood pressure at the coronary opening, thus decreasing coronary filling. However, rupture of any cusp at any place would have the same result depending upon the degree of insufficiency produced. There may be immediate fatal syncope or gradually developing circulatory failure; the prognosis depending primarily upon the size of the defect and secondarily upon the myocardial efficiency.

The duration of life was given by Howard[1] for thirteen of the proven cases. In one patient death was immediate; in another in a few hours; in a third but two hours intervened and in a fourth the patient survived three days. On the other hand, one patient survived ten years and another eleven years and one month which made a mean duration for the group of forty months for those that survived the immediate effects of the trauma. Both the patients described here died in a considerably shorter period of time.

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# Esophageal Hiatus Hernia*

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WHILE the problem of roentgenographic diagnosis of diaphragmatic hernias has been clarified in recent years, considerable interest is still occasioned by the unusual forms which the anomaly may take and the great discrepancy between clinical assumptions and roentgen data. Because many of these hernias are often entirely asymptomatic they may be discovered only incidentally at operation or postmortem examination. Those which produce symptoms do so either immediately after birth or remain undiscovered until late in life.

The following report is that of an esophageal hiatus hernia which was revealed on routine roentgen ray examination. Because of the bizarre character of the lesion it was considered of sufficient interest to warrant further investigation.

## CASE REPORT

A woman, married, aged forty-seven, was admitted to the hospital in September, 1945, complaining of epigastric pain associated with weakness and dizziness. Her medical history was irrelevant. The present illness began about seven to eight years before with vague epigastric distress unrelated to food but associated with heart burn and occasional vomiting. After a few years pain radiated to the right and posteriorly as well as to both shoulders. It was relieved somewhat by local application of heat, by lying on the left side or by leaning forward. During the past few years she experienced generalized abdominal distention relieved by local pressure. She complained of a constant sense of strain or discomfort in the epigastrium and lower part of the chest and lately suffered dizziness and weakness as well as dyspnea and palpitation on walking up one flight of stairs. There had been a gradual dietary intolerance particularly to fried foods, eggs and apples. She had no bloody stools but occasionally vomited bright red, blood-tinged food particles. Her weight had remained stationary during the past year.

Physical examination revealed a well nourished middle-aged, white woman in no apparent distress. The head and neck were normal except for extreme tenderness in the right supraclavicular fossa. There were no palpable nodes. The heart and lungs were apparently negative. The liver was palpable six fingers below the costal margin and extended laterally to the iliac crest. It was hard, nodular and not tender. No other masses were felt. Generalized tenderness was noted in the epigastrium.

On fluoroscopic examination no abnormality was noted in the upper halves of the thorax. The left diaphragm was normal in position and excursion but the stomach bubble was not in its usual position. Loculations of gas were seen below the left diaphragm which appeared to be loops of intestine. Several abnormalities were present at the base of the right lung. A large ovoid, opaque mass lay adjacent to the right cardiophrenic sulcus. It was triangular with the hypotenuse directed obliquely from the middle of the diaphragm to about the level of the base of the heart. (Fig. 1.) The diaphragm could be traced from the right costophrenic sulcus medially for about 5 cm. where its outline was lost. In the center of this mass or density the stomach bubble was seen to the right of the midline. The shadow of the gas bubble overlapped the right lower angle of the heart and through it the pulsation of the right cardiac border could be observed. In the right oblique and lateral projections, the aforementioned mass could be seen lying posterior to the heart and occupying the right paravertebral area. The visualized part of the right diaphragm was clear and regular. The heart was normally placed and forcible pulsations were noted at its borders.

* From the Department of Radiology, Hospital for Joint Diseases.

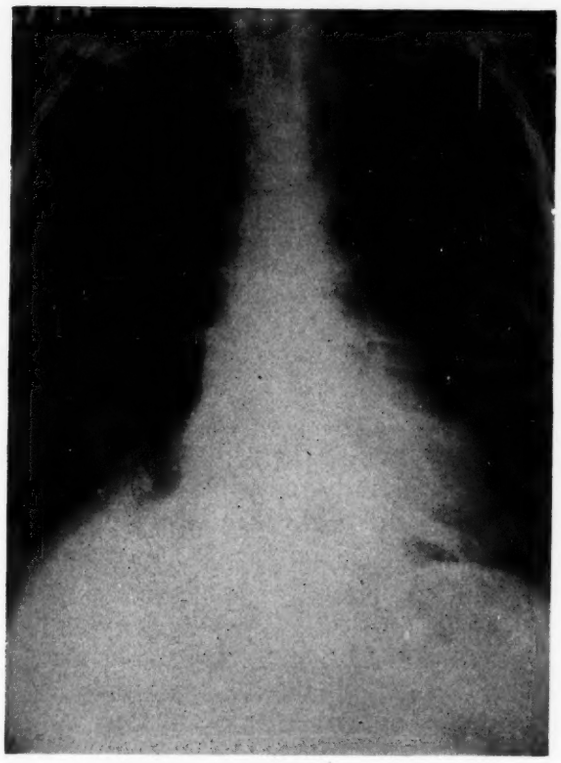

FIG. 1. Note obliquity of right diaphragm and triangular density in the cardiohepatic angle.

Administration of a small amount of barium mixture revealed the esophagus to be normal in size and shape. The opaque mixture was seen to descend to an area just above the orifice in the left leaf of the diaphragm where it turned sharply and passed posteriorly and upward to empty into what apparently was the cardia of the stomach lying above the upper border of the liver and to the right of the midline. (Fig. 2.) In the lateral projection the proximal part of the stomach was seen to lie posteriorly. It was "U-shaped," placed on its side with its upper arm above the level of the diaphragm, its lower arm below and its base directly to the right of the right paravertebral recess. (Fig. 3.) The barium mixture passed freely through the stomach and coursed downward and anteriorly through a narrowed channel which apparently was the duodenum or some part thereof. A small diverticulum was seen in the second part of the duodenum. The narrowed intestine passed downward into the pelvis where the mucosal pattern of the jejunum was identified. Roentgenograms confirmed the fluoroscopic diagnosis.

The roentgenoscopic and roentgenographic pictures presented a particularly

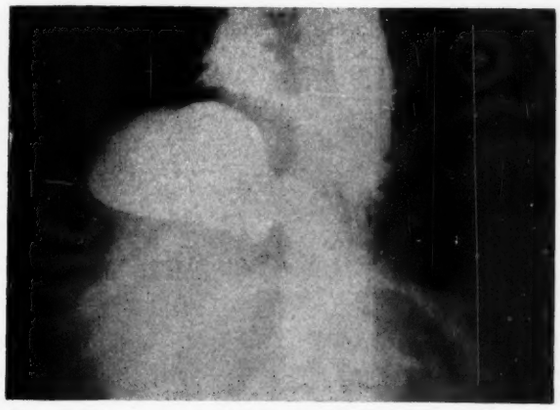

FIG. 2. The lower end of the esophagus deviates sharply to the right, posteriorly and upward to enter the cardiac extremity of the stomach. The major portion of the stomach is to the right of the midline. The pylorus and duodenum face to the left.

interesting problem in diagnosis and required a differentiation of the many varieties of diaphragmatic hernia in order to determine the category in an acceptable classification. Several classifications have been suggested usually based on the origin, structure or genesis of the defect. We have selected Harrington's[1] as representative and have modified it somewhat to conform to our conclusions.

CLASSIFICATION OF DIAPHRAGMATIC HERNIAS

1. Non-traumatic:
   - A. *Congenital:*
     - (1) Foramen of Morgagni (subcostosternal)
     - (2) Dome of diaphragm—absence of or gap left by incomplete hemidiaphragm; usually on the left side
     - (3) Pleuroperitoneal (foramen of Bochdalek)
     - (4) Esophageal hiatus:
       - (*a*) Congenital short esophagus
       - (*b*) Para-esophageal and esophageal hiatus hernias
   - B. *Acquired:*
     - (1) Through an area of embryonic fusion
     - (2) Through a congenital defect
     - (3) Esophageal hiatus
2. Traumatic—of various categories, including severe crushing injuires, gun-

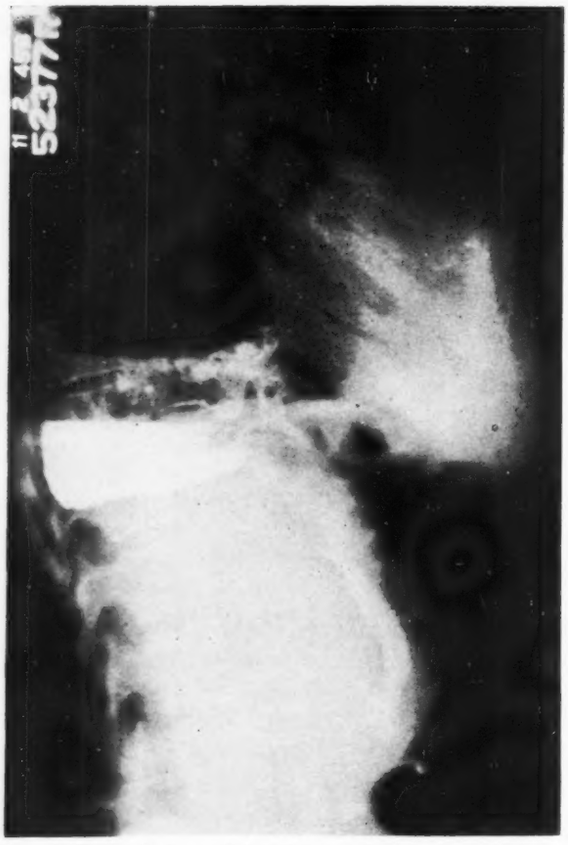

FIG. 3. Lateral view of the chest and abdomen showing the stomach in the posterior half of the thorax. Note that the lower pole of the stomach passes through the diaphragm and that the duodenum is anteriorly situated.

shot wounds, fracture of ribs, tear and rupture of subdiaphragmatic abscess.

We are concerned here solely with the non-traumatic group.

### DIFFERENTIAL DIAGNOSIS

The subcostosternal hernia occurs through an opening in the diaphragm immediately beneath the right side of the sternum and right costal margin, through the foramen of Morgagni. Robbins,[2] in reporting an example of this variety, placed emphasis on its roentgenographic characteristics and especially on the shadow which lies close to the anterior thoracic wall. Thus, the site of hernias of this variety serves to eliminate our case from further consideration of this group.

Herniations through the dome of the diaphragm or through the pleuroperitoneal hiatus may be difficult to differentiate from other varieties. Their site is significant to some extent, the first usually lying posteriorly and the second more laterally in the area of embryonic fusion of the diaphragmatic components. Accurate differentiation depends on the demonstration of the normal descent of the esophagus through the diaphragm, followed by herniation of the stomach through any of the aforesaid hiatuses. In our patient the esophagus, while of normal length, at no area passed through the diaphragm but instead moved posteriorly and upward to join the cardiac end of the stomach to the right of the midline. In a congenital short esophagus the stomach fails to descend below the diaphragm during embryonic development. It has been suggested that this form is not a true hiatus hernia but rather a congenital ectopia of the stomach caused by failure of descent during embryonic development.[3]

In our patient the esophagus was of normal length. In esophageal hiatus hernia the esophagus is seen to be of normal length and enters the stomach eccentrically. This is by far the most common form of diaphragmatic hernia, the categories of which are described extensively in surgical literature. The roentgenologist frequently notes variations in size and position of this hernial pattern. It involves more than the upper part of the stomach. Less frequently found hernias are those which consist of either one-half or else the entire stomach, with or without other abdominal organs. In the first variety the lower end of the esophagus actually passes through the diaphragm and enters the stomach somewhat eccentrically. The herniated part of the stomach rests beside the esophagus in the posterior mediastinum. Harrington terms this variety "para-esophageal hiatus hernia. "In herniation of greater degree a sufficient part of the viscus passes through the orifice in such a manner as to drag the abdominal part and perhaps some of the lower segments of the esophagus. The roentgenographic signs then vary with the *degree of herniation* and may include: (1) gas bubbles above the level of the diaphragm; (2)

normal length of the esophagus; (3) the lower end of the esophagus, which may be redundant and tortuous because of upward displacement; (4) the lower end of the esophagus which may be displaced laterally; (5) fixation of the cardia above the diaphragm; (6) constriction of the cardia; (7) altered mobility of the diaphragm; and (8) displacement of the heart. Feldman[4] points out that "in most instances the herniated portion lies to the left of the esophagus, somewhat posteriorly and as it increases in size approaches the midline, displacing the esophagus."

In our case of esophageal hiatus herniation the roentgenographic pattern revealed was as follows: (1) The stomach bubble was not in its usual position but above the diaphragm and posteriorly on the right side; (2) the esophagus descended to an area directly above the diaphragm and then passed sharply upward and posteriorly (Fig. 2); (3) the esophagus entered the cardiac end of the stomach above the diaphragm; (4) the stomach assumed a "U-shape" lying partly above and partly below the diaphragm; and (5) the duodenum passed from the right to the left, inclining downward and anteriorly through the diaphragm, its course beyond the pylorus apparently resting within the large hiatus.

## CONCLUSIONS

In considering the bizarre roentgenographic pattern and the possible mechanism involved, it would seem that at one time the stomach rested in its normal position below the diaphragm. Furthermore, it is probable that for some unexplained reason the stomach migrated upward, pulling with it not only the esophagus at its cardiac end but also its peritoneal attachments, thus displacing the splenic flexure and adjacent parts of the colon. Beginning perhaps as a minor para-esophageal herniation the stomach continued its movement in such a manner as to enlarge the previous hiatus to an extremely wide orifice extending from the site of the usual esophageal hiatus posteriorly and to the right. It was evident moreover that in its excursion the stomach rotated on its longitudinal axis with concurrent rotation on its transverse axis, coming finally to rest in the position it now occupied.

It is difficult to decide whether the primary defect was congenital or acquired. The absence of a history of trauma and of previous complaints, the possibility of an insidious onset and progression before reaching the overt clinical stage, caused doubt in regard to classification. Was a small para-esophageal hiatus hernia present at birth? Did it progress to this stage for forty years without inducing symptoms? Was there only a congenital defect of the hiatus wall at birth and were the clinical signs coincident with the onset of the process some eight years before? Were the stomach and its anatomic relations entirely normal until the onset of clinical signs eight years before?

After considering all the foregoing, we concluded that the correct classification of this anomaly probably was in the category of unusual, non-traumatic esophageal hiatus hernia.*

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* Since the completion of this report we were informed that the patient, while out of town, suddenly developed acute, upper abdominal distress and was admitted to a local hospital in a stuporous condition. The physical signs on admission suggested upper gastrointestinal obstruction. The patient never regained consciousness and died in about two days. Permission for postmortem examination was refused. So far as we could ascertain, no definite diagnosis was made. It is our impression that the cause of death was a volvulus of the stomach.

# Special Feature

## Western Society for Clinical Research

### First Annual Meeting Held in San Francisco November 7 and 8, 1947

Cholesterol Metabolism and Its Relationship to Atherosclerosis, Coronary Artery Disease, and Arteriosclerosis. *Lester M. Morrison, M.D.; Lillian Hall, M.D.;* and *Albert L. Chaney, Ph.D., Los Angeles, California.*

Blood serum cholesterol and ester levels in acute coronary thrombosis have been determined in some 500 cases at the Los Angeles County General Hospital.

These levels were compared to control cases in normals and in various diseases, such as hypothyroidism, cirrhosis of the liver, nephrosis, xanthomatosis, etc.

The cholesterol and ester levels were followed in coronary occlusion cases and in a normal series of controls.

These cholesterol and ester levels were then followed every six weeks in the Research Clinic after the administration of 6 Gm. of choline daily.

Cholesterol and ester levels were followed every six weeks in the Research Clinic—on high fat, low fat, high protein diets, and low protein diets to determine the influence of these diets on the cholesterol and ester blood levels.


SUMMARY

A consecutive unselected series of 200 patients with acute coronary occlusion was studied for blood cholesterol and cholesterol ester levels within forty-eight hours after hospital admission. In 68 per cent of seventy-five patients under sixty years of age with proven acute coronary occlusion hypercholesterolemia was present. In 52 per cent of 125 patients over sixty years of age with proven acute coronary occlusion a normal cholesterol level was found.

CONCLUSION

Coronary thrombosis in patients under the age of sixty is frequently associated with hypercholesterolemia and disturbances of cholesterol metabolism.


Protection Against Cyclopropane-Epinephrine Induced Cardiac Arrhythmias by Dibenamine and Other Agents. *Mark Nickerson, M.D.* (Introduced by H. H. Hecht, M.D., Salt Lake City.)

After induction of anesthesia with intravenous sodium pentothal (ave. 20 mg./Kg.), dogs were maintained on a 30 per cent cyclopropane-70 per cent $O_2$ mixture administered by endotracheal catheter with inflated cuff. After equilibration for thirty minutes, a standard challenge dose of 10 mg./Kg. epinephrine was injected intravenously in fifty seconds. Continuous standard-lead electrocardiograms were recorded during the period of epinephrine injection and until the cardiac rhythm returned to normal. Protective agents were administered ten to thirty minutes before the epinephrine.

About 25 per cent of unprotected animals developed ventricular fibrillation and the remainder showed long periods of ventricular extrasystoles and ventricular tachycardia. Dibenamine (20 mg./Kg.) almost completely eliminated all irregularities leaving a sinus tachycardia as the only response to the epinephrine. Protection was equally effective when challenge doses of 100 and 1000 mg./Kg. were employed.

Priscol (20 mg./Kg.) was only slightly less effective than dibenamine when tested with 10 mg./Kg. of epinephrine, but gave little protection against larger doses.

Demerol (10 mg./Kg.) and large doses of atropine sulfate (1 mg./Kg.) gave significant, but somewhat variable protection while quinidine sulfate (5. mg./Kg.), procaine hydrochloride (16 mg./Kg.) and ergotamine tartrate (0.25 mg./Kg.) had insignificant effects. Smaller

doses of atropine sulfate (0.1 mg./Kg.) and bilateral vagotomy did not protect, indicating that the protection afforded by massive doses of atropine is not due to its action in blocking vagal impulses.

No agent was found capable of restoring normal cardiac rhythm after ventricular fibrillation was established, even when given by intracardiac injection and accompanied by cardiac massage.

Dibenamine blocks most of the excitatory effects of epinephrine and sympathetic nerve impulses, but it has been shown not to sensitize animals to hemorrhagic shock. Its clinical use to prevent cardiac arrhythmias in patients under cyclopropane anesthesia is suggested.

ON THE USE OF AMMONIUM CHLORIDE BY VEIN IN RESISTANT EDEMA AND OLIGURIA; A PRELIMINARY REPORT. *Ferdinand Ripley Schemm, M.D., Great Falls, Montana.*

Ammonium chloride by vein was given fifty-two times to twenty patients in an effort to relieve edema or oliguria which had proven resistant to usual measures, 4.6 Gm. of ammonium chloride and 20 Gm. of dextrose in 1,000 cc. of distilled water appeared *in vitro* to give a maximum concentration of ammonium chloride without hemolysis and a maximum diuretic effect with a minimum of unpleasant reactions. The volume of the solution used was 1,000 cc. in eleven instances and 500 cc. in forty-one instances. One patient received eleven venoclyses of 500 cc. in four days.

The use of ammonium chloride was limited to two classes of patients; those who were obviously near the end of a long chronic illness and on whom the immediate effect of the drug on edema was observed, and those whose critical state depended chiefly on the edema or oliguria or anuria which had resisted other measures. In twelve cases, only one of them from the hopeful class, the ammonium chloride had no effect on the edema or oliguria. Severe reactions characterized by pallor, sweating and retching, were observed in five of these twelve cases, as well as in one of the eight cases that responded. In eight cases, four from the first class and four from the second class, the ammonium chloride appeared to be solely responsible for instituting a beneficient diuresis and/or the clearing of edema. The four from the hopeful class recovered and are well or active after from one to three years.

The carbon dioxide combining power and plasma chlorides obtained before venoclysis failed to indicate the presence of antecedant alkalosis in those cases which responded well, or of antecedent acidosis in those which reacted badly; and any degree of acidosis that may have been induced by the venoclysis was not detectable by these determinations. It is hoped that investigations now in progress may clarify the indications for the use of ammonium chloride by vein.

STUDIES ON THE COLLATERAL CIRCULATION OF HEARTS WITH ACUTE CORONARY OCCLUSION. *Myron Prinzmetal, M.D.; H. C. Bergman, Ph.D.; H. E. Kruger, M.D.; Lois Schwartz, M.D.; Benjamin Simkin, M.D.;* and *Sidney S. Sobin, M.D., Los Angeles.*

Radioactive red cells were injected intravenously into moribund patients and the distribution of the red cells in the heart was determined after death by means of direct Geiger counts and radioautographs of the heart. In two human hearts with myocardial infarction, the number of red cells was the same in the infarcted and normal areas of the heart.

These unexpected findings prompted a series of acute experiments in dogs. A branch of the left coronary artery was ligated. Radioactive red cells were injected intravenously and later the heart was stopped by freezing. The distribution of red cells was determined. The red cells were distributed throughout the entire heart within one minute after injection. The quantity of circulating blood in the pericardial surface of the ischemic area was equal to that of the surrounding control areas.

In order to determine if collateral blood came from Thebesian vessels or anastomoses from other coronaries, fluorescein was injected intravenously in animals with ligated coronary arteries. The fluorescein was seen to enter the ischemic area from contiguous areas.

It was therefore concluded that the collateral circulation to the ischemic area was derived from anastomotic channels between the coronary arteries.

HEMOLYTIC ANEMIAS, CONGENITAL AND ACQUIRED. *Robert S. Evans, M.D., San Francisco.*

Observations of the longevity of transfused cells in patients with hemolytic anemia have

demonstrated a fundamental difference in the pathogenesis of acquired hemolytic anemia with spherocytosis and congenital hemolytic jaundice. Normal erythrocytes have a reduced survival time in patients with acquired hemolytic anemia, indicating the presence of a hemolysin active against all erythrocytes. On the other hand, transfused cells have a normal survival time in patients with congenital hemolytic jaundice indicating that the accelerated hemolysis in this disease is due to a defect in the patient's erythrocytes.

The presence of an immune body type of hemolysin can be demonstrated on the surface of erythrocytes in acquired hemolytic anemia by the susceptibility of the cells to agglutination in an anti-human globulin rabbit serum. Normal erythrocytes and those from patients with congenital hemolytic jaundice do not agglutinate in the immune serum. The hemolytic antibody found in the acquired form can be eluted from the cells and transferred to normal cells in vitro.

Eight patients with acquired hemolytic anemia have been studied with the above technics. A hemolysin has been demonstrated in each case, by one or both methods. Studies following splenectomy indicate that response to splenectomy depends on the cessation of production of the immune body. Studies of three patients with congenital hemolytic jaundice have failed to demonstrate the presence of a hemolytic antibody. In one patient a hemolytic crisis followed transfusion but it was evident that only the patient's own cells and not the transfused cells were involved in the rapid hemolysis.

PATHOGENESIS OF INTRASPLENIC OVARIAN TUMORS IN RATS. *Gerson R. Biskind, M.D.* and *Richard Pencharz, Ph.D., San Francisco.*

The transplantation of an ovary into the spleen of a castrate rat places that ovary in a unique hormonal situation. It has been shown previously that the liver is the site of inactivation of the sex hormones. Transplantation of the ovary into the portal circulation permits the hormones it elaborates to pass directly to the liver where they are inactivated. Thus, there is present active ovarian tissue in an animal that exhibits castrate features particularly in the vagina, uterus and hypophysis. The transplanted ovarian tissue responds with excessive growth to gonadotrophic stimulation from the hypophysis. After varying periods up to one year, the transplanted organ becomes transformed into a tissue which has the histologic appearance of a neoplasm. The most common histologic pattern observed is a luteoma; in addition, in many of the luteomas there are nests of proliferating small cells that simulate the pattern of a granulosa cell tumor.

A series of rats have been prepared by operation and then sacrificed at regular intervals to determine the consecutive histologic changes that take place in the transplanted ovary. From these observations, the histogenesis of this tumor will be described and illustrated by lantern slides. Variations in the histologic pattern of the tumor will also be illustrated. Other factors concerned in the pathogenesis of the tumor will be discussed.

PLASMA CELL RESPONSE IN IMMUNIZED ANIMALS. *Thomas F. Dougherty, M.D., Salt Lake City.* (Introduced by H. H. Lerner, M.D.)

Since numerous plasma cells are found in tissues of hyper-immunized animals it has been suggested that these cells are concerned with the production of antibodies.

It was noted in this laboratory that the numbers of plasma cells increase in the tissues of animals following successive dosages of antigens. In order to determine whether the occurrence of plasma cells was correlated with the production of antibody, mice of the CBA strain were given a single injection of either sheep red corpuscles or of staphyloccus toxin. Serologic and histologic studies were carried out at intervals of two hours for the first day and daily for six days thereafter. Antibody to either of these antigens appeared on the fourth day and maximal titers were found on the seventh day. Another group of animals received a second dose of the same anitgen on the seventh day.

Immediately following the initial immunizing injection a slight increase in numbers of plasma cells occurred but on the seventh day were not more frequent than in the non-immunized animal. Lymphocytes contained antibody on the seventh day. Six hours after the second injection of the same antigen there was a marked increase in numbers of typical Marschalko type plasma cells derived from lymphocytes in the lymphatic tissues.

Although plasma cells may contain antibody they are primarily reaction cells to antigens to which the animal has been sensitized. The Marschalko plasma cell is very probably a

morphologic alteration due to an antigen antibody reaction within or at the surface of a lymphocyte which contains antibody to a specific antigen.

USE OF ALLANTOIN AS A MEASURE OF GLOMERULAR FILTRATION IN THE RAT, DOG AND MAN. *Meyer Friedman, M.D.; Sanford O. Byers, M.D.;* and *Paul Abrams, M.D., San Francisco.*

Twenty-one allantoin clearances were done on twenty normal rats and compared with the creatinine clearances of seventeen other rats. The respective clearances were 33.7 and 34.6 cc. per 100 Gm. body weight per hour, indicating the essential similarity of the two clearances.

Twenty allantoin and twenty creatinine clearances were performed simultaneously on five normal dogs. It was found that the average allantoin clearance (89.9 cc. per sq. M. per minute) was approximately the same as the average creatinine clearance (89.3 cc.).

Five normal men were given 10 Gm. of allantoin by mouth and two hours later, clearance studies were done. It was found that the average clearance was 124.6 cc. per minute per 1.73 sq. M. This is of the same magnitude as the inulin clearance (125.0 cc. in our previous studies).

In view of the fact that the allantoin clearance was similar to the creatinine clearance in rats and dogs and of the same value as the inulin clearance in man, it is believed that the rate of renal excretion of allantoin may be used to study the rate of glomerular filtration in both the animal and man. The complete absence of toxicity following the oral ingestion of allantoin, its much greater solubility than inulin in urine, the avoidance of intravenous administration and its easier chemical determination—all of these things make the allantoin clearance a more suitable clinical test for estimation of glomerular filtration than the inulin clearance.

RESPIRATION OF HUMAN PLACENTAL TISSUE FROM NORMAL AND ECLAMPTIC PREGNANCIES. *Hal P. James, M.D.; Henry W. Elliott, Ph.D.;* and *Ernest W. Page, M.D., San Francisco.*

The oxygen consumption of freshly delivered human placental tissue was studied by the direct method of Warburg. The general relationship between placental age and $CO_2$ established by Wang and Hellman was confirmed. Endogenous $CO_2$ values ranges from7.01 at forty-seven days' conception to a mean of 1.9 at term. In comparison to the normal placenta of corresponding age, placental tissue from women with pre-eclampsia or eclampsia showed a marked decrease in oxygen consumption, an effect not observed in other hypertensive complications of pregnancy. The relationship which this finding bears to the known histologic changes of the eclamptic placenta is discussed.

EFFECTS OF TEMPERATURE AND EXERCISE ON VENOUS PRESSURE IN THE FOOT WHEN IN THE ERECT POSTURE. *James P. Henry, M.D., Los Angeles.*

The venous pressure in the foot in the erect posture was measured by cannulation to a vein in the dorsum. The cannula was attached either to a water manometer or to a pressure sensitive tipped catheter which permitted free movement of the foot. It was found that the pressure is dependent upon the environmental temperature as well as upon the activity of the limb. When the subject is still, the venous pressure attains approximately the full hydrostatic head regardless of the environmental temperature. Standing-walking at an environmental temperature of 65° to 75°F. will lead to a mean venous pressure at or less than knee level. The same exercise when the foot temperature is maintained at 104° to 113°F. will produce a mean venous pressure which supports a blood column extending up to the inguinal level. The mechanism of development of the dependent edema observed in hot weather may be related to these observations. It is suggested that in these conditions blood flow increases due to vasodilation and the rate of pumping of blood and lymph by muscle action does not increase correspondingly. As a result the mean venous pressure may rise significantly above the normal level and edema develop.

EFFECTS OF LOCAL VENOUS CONGESTION ON CARBON MONOXIDE-AVAILABLE VOLUME AND ON MIXING CURVES OF CARBON MONOXIDE AND T-1824 IN VENOUS BLOOD. *Ellen Brown, M.D.; James Hopper, Jr., M.D.; Charles Mudrick, M.D.;* and *John J. Sampson, M.D.; San Francisco.*

Studies were made using a closed system $CO_2$ method to determine (*a*) whether total blood

volume can be measured when in portions of the vascular tree circulation is slowed by local increases of venous pressure, and (*b*) whether localized congestion affects mixing of CO or T-1824.

CO-available erythrocyte mass was calculated from hematocrit and CO content of blood samples; blood and plasma volumes were accurate only insofar as venous hematocrit approximated body hematocrit. Congestion was produced by inflation of pneumatic cuffs surrounding both thighs and one arm to between 0 and 10 mg. Hg below diastolic blood pressure. Three normal human subjects were used for each of the following experiments:

1. After ten minutes of prior congestion, CO-available volume was determined during congestion and at intervals after release of cuffs. CO-available erythrocyte mass ten to eighteen minutes after release was not significantly greater than during congestion.

2. Venous blood concentrations were measured at thirty and sixty-second; subsequently at longer intervals after introduction of CO and T-1824. Mixing curves were similar whether made at rest or during congestion.

3. To determine volumes of blood accumulated in limb veins during congestion, cuffs were inflated suddenly to 200 mm. Hg after ten minutes of venous congestion. Six to eleven minutes after release of cuffs CO-available blood volume was 1,120 to 1,630 cc. greater than during arterial occlusion.

It is concluded that blood accumulated in vascular reservoirs of the extremeties is accessible to CO and T-1824. Venous stasis involving at least a quarter of total blood volume could not be detected by the methods employed.

EXPERIMENTAL LESIONS OF THE PULMONARY ARTERY ASSOCIATED WITH PATENT DUCTUS ARTERIOSUS. *Sanford E. Leeds, M.D., San Francisco.*

Experimental patent ductus arteriosus may be produced in dogs by a side-to-side anastamosis between the aorta and pulmonary artery or by an end-to-end anastamosis between the subclavian or innominate arteries and the pulmonary artery. (Leeds, *Am. J. Physiol.*, 1943.)

In chronic experiments fibrotic intimal plaques may be found on the wall of the pulmonary artery opposite the opening of the ductus. The plaques consist of collagenous and reticulum fibers and a few flattened fibrocytes. Lipid material is not demonstrated. Possible explanation of the pathogenisis of the plaques and their relation to those described in man in association with patent ductus arteriosus will be discussed. Artificial ductus arteriosus is now produced in children with pulmonic stenosis to relieve the latter condition and lesions on the pulmonary artery may be expected to follow on the basis of the experiments outlined above. Lantern slides will be presented.

EXPERIMENTAL CARDIAC HYPERTROPHY: THE ACUTE EFFECTS OF PULMONARY AND AORTIC STENOSIS. *Arthur Selzer, M.D.* and *Frank Gerbode, M.D., San Francisco.*

Cardiac hypertrophy in animals has been produced successfully by various methods, mostly reproducing clinical conditions known to be associated with enlargement and hypertrophy of the heart. Little information, however, is available as to the speed with which the heart muscle grows in response to a stimulus.

The purpose of this study was to investigate the degree of hypertrophy developing acutely after experimental aortic or pulmonary stenosis. A method was developed of constricting the first portion of the aorta or pulmonary artery, respectively, by a band of fascia lata with a gradually progressive stenosis over a period of about forty-five minutes. This method led to a considerable reduction in mortality from corrosion of the constricted vessel and from cardiac failure.

Successful stenosis was produced in fourteen dogs, that of the aorta in twelve and the pulmonary artery in two. The animals were sacrificed in two or three weeks. In seven dogs the degree of hypertrophy was measured by the heart-weight-to-body-weight ratio, and the othes seven were puppies with identical litter mater used as controls. At autopsy stenosis was found to be mild in five animals and moderate in nine. All animals with moderate stenosis showed definite hypertrophy with a maximum of 65 per cent increase over control animal. Histologic examination revealed marked increase in the size of muscle fibers.

These results were compared with experiments of Herrmann and Holman who used similar methods but extended their experiments for many weeks and months. It is concluded that the degree of cardiac hypertrophy developing within three weeks is comparable to results of experiments extending for long periods of

time. This implies that hypertrophy of the heart is an acute process with most of the growth occurring within a short time after the stimulus for hypertrophy is established.

ARREST OF THERMAL PANTING BY TYPHOID-PARATYPHOID VACCINE ADMINISTRATION. *V. E. Hall, M.D.; F. A. Ellis, M.D.; B. Panzer, M.D.;* and *R. Grant, M.D., San Francisco.*

In fever the activity of the physiologic mechanisms for the dissipation of heat is reduced. In furred animals panting is important among these mechanisms. In a study of fever evoked in rabbits by the intravenous injections of typhoid-paratyphoid vaccine, we have found that thermal panting is arrested about fifteen minutes after vaccine administration. Panting can be restored, however, by increasing the body temperature to a new high level. Thus the body temperature threshold for panting is elevated by the vaccine. Since the respiratory response to inhalation of 5 per cent $CO_2$-95 per cent $O_2$ is not impaired by vaccine administration, it is improbable that the vaccine depresses the medullary respiratory center. Whether panting is arrested by depression of the pontine pneumotaxic center or a higher respiratory mechanism is now under investigation.

PERTUSSIS AGGLUTINOGEN SKIN TEST. *John J. Miller, Jr., M.D.; Mary L. Ryan, M.D.;* and *Edward Havard, M.D.; San Francisco.*

One hundred children who had received H. pertussis vaccine in variable dosage two months to eight years previously were skin tested with the acid extracted H. pertussis agglutinogen of Felton, Smolens and Mudd. Determinations of their serum agglutinins for H. pertussis were performed concurrently with a technic which has been correlated with clinical immunity. A significant association was found between "positive-immune" skin reactions and high agglutinin titers consonant with clinical immunity. On the other hand there was no significant association between "negative-susceptible" skin reactions and low serum antibody. Ten per cent of the children had "negative-susceptible" skin reactions while carrying high titers of agglutinins.

In children who had received vaccine more than a year previously a positive correlation between the total dose of vaccine and the degree of skin reactivity was observed.

In children who had received a total dose of more than 80 billion (saline suspended) H. pertussis, it was found that skin hypersensitivity did not decrease with time until four years after the administration of vaccine. Serum agglutinin levels roughly paralleled the skin reactions.

The skin tests stimulated an increase in serum antibody in 68 per cent of fifty children whose sera were titrated a week thereafter. Intradermal injections also increased the reactivity of the skin itself. Agglutinogen is therefore antigenic.

Ten children with unquestionable histories of pertussis during the past twelve years were skin tested. In only one was a "positive-immune" reaction elicited.

CONCLUSION

Skin hypersensitivity to acid extracted H. pertussis agglutinogen is a valid index of immunity in children who have received H. pertussis vaccine in the past. A lack of hypersensitivity, however, is not necessarily an index of susceptibility. In children who have recovered from an attack of pertussis, testing with agglutinogen is misleading (and unnecessary) as many individuals may exhibit no hypersensitivity.

EFFECT OF BENZOIC ACID ON PENICILLIN BLOOD LEVELS AND RENAL FUNCTION. *John F. Waldo, M.D.* and *Wan Ching Lu, M.S. Salt Lake City.* (Introduced by M. M. Wintrobe, M.D.)

Daily penicillin levels were measured in early luetics receiving rapid treatment without arsenicals. During a four-day control period daily penicillin levels and blood urea nitrogens as well as the initial endogenous creatinine clearance were determined. Following this the patients were given 12 Gm. of benzoic acid per day for five days, an amount about as great as could be tolerated. During this time penicillin levels and blood urea nitrogens were determined daily. Creatinine clearance was repeated at the end of the period and when possible on the second day of benzoic acid administration.

There was no consistent alteration in the blood penicillin levels associated with the administration of benzoic acid. In a few cases the blood urea nitrogen rose temporarily but usually it returned to normal even though the benzoic acid was continued. The creatinine clearance showed no significant variation at any time. It is concluded that benzoic acid, given in the stated amount, is ineffective in raising the blood

level of the penicillin. There appears to be no permanent damage to the kidney by the use of this drug.

USE OF INFLUENZA VIRUS VACCINE IN CHILDREN. *Henry B. Bruyn, M.D.; Gordon Meiklejohn, M.D.;* and *Henry D. Brainferd, M.D., San Francisco.*

The extensive use of the combined Type A and Type B Influenza Virus Vaccine in adults has established the dosage and expected serologic response. This information is at present not available for its use in children, save for arbitrary dose schedules and one report giving such a high incidence of reactions as to contraindicate its use.

The intradermal route of inoculation has been used for this vaccine in adults with satisfactory serologic response and rare reaction.

The present investigation concerns the inoculation of seventy-nine children, aged one year to fourteen years, using this vaccine subcutaneously and intradermally in a variety of doses, and measuring the serologic response.

The incidence of febrile reaction to subcutaneous vaccine was 59 per cent, almost all involving temperatures over 101°F. and obvious symptoms. Following 0.1 cc. intradermally, the incidence was 26 per cent and was 36 per cent after 0.1 cc. twice, separated by three days rarely with temperatures over 101°F. and never with overt symptoms.

The fold increase in antibody to Type A and Type B Influenza following 0.5 cc., 0.25 cc.and 0.125 cc. subcutaneously and 0.1 cc. intradermally was equal or better than the results reported for adults. The response to 0.1 cc. intradermally given twice was most consistent and over twice the adult response.

The average post-vaccination titre to the two types was as high or higher than in adults, following 0.5 cc. and 0.25 cc. subcutaneously and 0.1 cc. twice intradermally.

Averaging all routes and doses, children under seven years of age had less increase and lower final titres than those over seven.

The higher pre-vaccination titres yielded smaller increases in antibody.

CLINICAL VALUE OF UNIPOLAR EXTREMITY LEADS. *Maurice Sokolow, M.D., San Francisco.*

The practical clinical value of multiple precordial leads has been clearly established. Not so well appreciated has been the practical aid obtained from unipolar extremity leads. A study was made in 1,000 patients of the unipolar leads with particular emphasis on their value in providing information not obtained from the standard limb and unipolar precordial leads. The findings are summarized as follows:

1. The presence of a significant Q wave in lead $aV_L$ may be the only clue to lateral myocardial infarction and indicate the advisability of high precordial leads in addition to the usual positions. The standard limb and six precordial leads may be normal or, if abnormal, of no characteristic pattern. Wilson, as well as Myers, has also called attention to the value of lead $aV_L$ in the diagnosis of lateral myocardial infarction.

2. A study of the Q wave in lead $aV_F$ is often decisive in the interpretation of Q wave in standard lead III. In posterior myocardial infarction, the Q wave reflecting potential changes from the basal surface of the heart is transmitted to the left leg and it is only when the Q wave in III is due to a significant Q wave in $aV_F$ that the $Q_3$ is diagnostic.

3. ST-T changes in $aV_L$ (horizontal hearts or $aV_F$ (vertical hearts) may be the first sign of left ventricular hypertrophy and may precede the ST-T abnormalities in $V_5$, $V_6$ or the standard limb leads.

4. Abnormalities in lead $aV_L$ typical of left ventricular hypertrophy or left bundle branch block may occur with normal appearing $V_5$ and $V_6$ if (a) the electrodes were placed too far to the right or (b) the transitional zone is displaced to the left.

5. In progressive left ventricular hypertrophy, ST-T abnormalities first appear in $aV_L$ or $aV_F$ and later in $aV_R$. The presence of an abnormal upright T in $aV_R$ is helpful evidence of a more advanced degree of hypertrophy.

6. Questionably abnormal right and left axis deviation may be shown by unipolar limb leads to be due to marked vertical or horizontal position of the heart, and in association with the precordial leads may differentiate normal from abnormal axis deviation.

7. Unusual rotation of the heart may at times be clarified by a study of the unipolar limb leads.

8. The electrocardiographic position of the heart, as obtained by unipolar limb leads, may clarify atypical abnormalities in the standard leads such as: (a) ST-T changes in lead II and III without axis deviation in left ventricular

hypertrophy in vertical hearts; and (b) Q waves in lead I instead of II and III in posterior myocardial infarction in horizontal hearts.

OBSERVATIONS ON THE HUMAN HEART DURING INDUCED HYPOXIA (THE ISCHEMIA-INJURY PATTERN). *Hans H. Hecht, M.D.; Junior A. Abildskov, M.D.; Robert C. Bolin, M.D.,* and *Ferne S. Focht, M.D., Salt Lake City.*

One hundred thirty-five patients were subjected to inhalation of a gas mixture consisting of 10 per cent oxygen and 90 per cent nitrogen for twenty minutes or less. Thirty-six tests were performed on presumably normal individuals, fifty-five on patients with signs and symptoms of coronary insufficiency and forty-four on patients who had suffered one or more episodes of proven myocardial infarction. No adverse reactions were encountered. A sudden fall in arterial pressure occurred in eight patients and necessitated interrupting the test.

In this report only the electrocardiographic changes observed are to be discussed. Levy's standardized technic was replaced by a more flexible system which included a number of semidirect unipolar leads, unipolar and bipolar limb leads. This modification permitted a detailed analysis of site, size and penetration of the anoxic regions not possible by Levy's method. Phases of ischemia and phases of injury similar to those demonstable in animal experiments (Bayley) were readily recognized. Subendocardial involvement was contrasted with epicardial lesions. All changes observed were quickly reversible.

The following conclusions appear justified: (1) The phase which can be induced during hypoxia indicates the severity of the underlying pathologic process. (2) Coronary insufficiency may be confined to certain myocardial regions and may leave other sections uninvolved. By the use of the technic proposed, the location, depth and extension of the abnormal zone can be demonstrated. (3) In patients who have suffered from myocardial infarction failure to alter the resting pattern suggests that adequate collateral circulation has been established. (4) Reversal of the electrocardiogram taken over the infarcted region from the ischemic to the injury pattern signals inadequate collateral circulation. (5) Ischemic areas may appear during the test at sites remote from a previously infarcted region. They may be responsible for residual anginal pain following occlusion of one coronary artery.

The method as outlined permits a rational interpretation of coronary artery disease. The test has prognostic value.

TREATMENT OF GRAVES' DISEASE WITH RADIOIODINE. *Earl H. Miller, M.D.* and *Mayo H. Soley, M.D., San Francisco.*

Iodine$^{131}$ (half life of eight days) has been administered to fifty-six patients with Graves' disease. Thirty-six of these patients have been followed sufficiently long to warrant evaluation of this method of therapy.

Three patients have been followed since October 12, 1941. Two have been normal for over five years; the third is normal except for questionable mild hypothyroidism. Of three other patients treated late in 1941 and early in 1942, two could not be followed and the third died of cerebral embolism during an attack of auricular fibrillation.

Thirty-three patients have been treated since July, 1945, and have been studied for a minimum period of six months and maximum of twenty-seven months. Of these, twenty-five patients have been classified as satisfactory in terms of their response. The average basal metabolic rate, protein-bound iodine, size of thyroids, time to return to normal and dose of Iodine$^{131}$, are as follows:

| | Before Treatment | After Treatment |
|---|---|---|
| BMR | +28% | −10% |
| PBI | 10.7 microgram % | 5.7 microgram % |
| Thyroid | 31 Gm. | 13 Gm. |

Time to return to normal: 3.6 months
Dose of $I^{131}$: 2,726 microcuries

Eight patients were classified as unsatisfactory either because they took too long to return to normal or have not yet returned to normal.

| | Before Treatment | After Treatment |
|---|---|---|
| BMR | +43% | +10% |
| PBI | 12.9 microgram % | 6.9 microgram % |

| | Before Treatment | After Treatment |
|---|---|---|
| Thyroid | 43 Gm. | 22 Gm. |

Dose of $I^{131}$: 5,537 microcuries

CHRONOLOGIC SEPARATION OF WATER AND CHLORIDE DIURESIS IN NEPHROTIC SYNDROME. *David A. Rytand, M.D., San Francisco.*

In a girl, aged four years, the nephrotic syndrome (pure lipoid nephrosis?) began abruptly during a serum sickness-like reaction to beesting. Early in the course of the syndrome, events moved quickly; it was then possible to examine individually some eighty-five consecutively voided specimens of urine (only a few were lost) through three spontaneous cycles of exacerbation and remission within a short time. Determinations included specific gravity, pH, and rates of excretion of water, chlorides, protein and formed elements.

In general, a rise of urinary pH was the earliest indication of approaching remission. This was soon followed by water diuresis. Finally the rate of chloride excretion increased, sometimes more than twenty-four hours after urine flow had become elevated. The time at which proteinuria decreased was variable within this sequence, and the numbers of formed elements were even more capricious.

Other workers have similarly shown chronological differences in behavior of water and of electrolytes (*a*) as edema collects during drug fever and (*b*) during the action of diuretics in patients with congestive heart failure.

The present findings suggest separate abnormalities in the renal excretion of water and of chlorides in the nephrotic syndrome.

EFFECTS OF LIPOTROPHIC AGENTS ON THE PROTEIN BALANCE IN PATIENTS WITH LIVER DAMAGE. *Laurence W. Kinsell, M.D.; George D. Michaels, M.D.; Harry A. Weiss, M.D.* and *Harry C. Barton, M.D., Oakland.*

In view of the role of choline and methionine in the prevention and treatment of liver damage in experimental animals, it was decided to attempt to evaluate the effects of these agents upon patients with liver disease. One such investigative effort was that of the determination of the effects of these agents upon the protein balance in such individuals.

The data here presented indicate that both methionine and choline will, in certain circumstances produce a strongly positive nitrogen balance. The theoretic considerations involved in these findings are discussed.

PSYCHODYNAMIC AND HYPOTHALAMO-HYPOPHYSIAL ASPECTS OF FERTILITY. *Harry B. Friedgood, M.D., Los Angeles.*

Correlation of the available anatomic, physiologic and clinical data discloses that the nervous system influences the functional activity of the adenohypophysis, probably through neurohumoral means. The hypothalamo-hypophysial area plays an important role in the pathogenesis of impotence and in the mechanism by means of which emotional conflicts disturb gonadal function.

STUDIES ON ACTIVE IMMUNITY AGAINST TETANUS. *John J. Miller, Jr., M.D.* and *Mary L. Ryan, M.D., San Francisco.*

Tetanus antitoxin titrations in children following basic immunization with fluid alum precipitated and aluminum hydroxide absorbed tetanus toxoid were compared. Over a period of four years the last mentioned was found to produce and maintain higher levels of antitoxin.

The speed of increase in circulating antitoxin in previously immunized individuals following reinjection with fluid, alum precipitated, and aluminum hydroxide adsorbed tetanus toxoid was compared. Fluid toxoid was found to be most rapidly effective.

The laboratory and field evidence (from the British Army) for and against the use of tetanus antitoxin in actively immunized individuals is briefly reviewed.

The application of this information to the treatment of contaminated wounds in ex-service men (and tetanus immunized children) is discussed. It is concluded that (1) routine bienniel reinjections with adsorbed toxoid be encouraged in ex-service men, (2) fluid toxoid is the agent of choice as a wound booster, (3) prophylactic antitoxin is not contraindicated and occasionally may be advisable as in cases of compound fractures or gunshot wounds.

COMPARATIVE STUDY OF THE EFFECTS OF ADMINISTRATION OF LARGE DOSES OF HORSE SERUM AND HUMAN ALBUMIN TO RABBITS WITH REFERENCE TO FORMED ELEMENTS OF THE BLOOD, PLASMA PROTEIN CONSTITUENTS AND IMMUNOLOGIC CHANGES. *B. V. Jager, M.D.* and *R. J. Nelson, M.D., Salt Lake City.*

The clinical and experimental observations that serum sickness may result in pathologic

lesions simulating those of periarteritis nodosa and acute rheumatic fever suggest that a study of certain hematologic and immunologic aspects of experimental serum sickness in animals might offer useful information.

One group of ten rabbits was given intravenously, a single large dose of horse serum (mixed antigen); a similar group received a single large dose of human albumin (relatively homogeneous antigen); while a third group of equal number served as controls. Specimens of blood for various studies were obtained repeatedly from each group during a seven-week period following injection of foreign protein.

With the exception of a transient lymphopenia which followed injection of albumin or horse serum, the injection of foreign proteins did not lead to significant changes in the packed red cell volume, total and differential leukocyte counts and the reticulocyte response when contrasted to the control group.

In spite of inherent difficulties attributable to animal variation, the rabbits receiving horse serum showed a moderate increase in plasma fibrinogen and a delayed rise in total globulin and "gamma globulin" (determined chemically). No significant reduction in serum albumin occurred. By contrast no impressive changes occurred in these protein constituents in the animals receiving human albumin.

After injection of antigen, circulating precipitinogen persisted much longer and precipitins appeared earlier in the group receiving horse serum than in the one receiving human albumin. Antibodies to a globulin fraction of horse serum seemed to develop earlier than antibodies to horse serum albumin.

The total quantitative serum hemolytic complement decreased following administration of horse serum but not after injection of human albumin.

COMPARISON OF CHEMICAL DETERMINATIONS OF SERUM ALBUMIN CONCENTRATION WITH CORRESPONDING ELECTROPHORETIC PATTERNS. *T. B. Schwartz, M.D., Salt Lake City.* (Introduced by B. V. Jager, M.D.)

Numerous observers have shown that the commonly used sodium sulfate precipitation methods of Howe for the determination of serum albumin concentration gives falsely high values when compared to those obtained by electrophoresis. In view of the obvious need for a simple, easily executed reasonably reliable clinical procedure for estimating albumin concentration in normal and pathologic sera, the results obtained by three precipitation technics were compared with values obtained by electrophoresis. All four procedures were carried out on aliquots of individual samples of both normal and abnormal sera, the albumin concentration ranging from 17 to 64 per cent in the series of sera tested.

As noted by others, the Howe method (21.5 per cent sodium sulfate) yielded serum albumin concentrations that were 4 to 20 per cent higher than those determined electrophoretically.

The methanol precipitation procedure described by Pillemer was found to be technically difficult to control and, in pathologic sera, gave results which were consistently lower than the electrophoretic values.

Precipitation of serum globulins by saturated magnesium sulfate (Popjak and McCarthy) was found to be a reliable and relatively accurate method for serum protein partition, yielding serum albumin values which correlated closely with those obtained by electrophoresis.

# Book Review

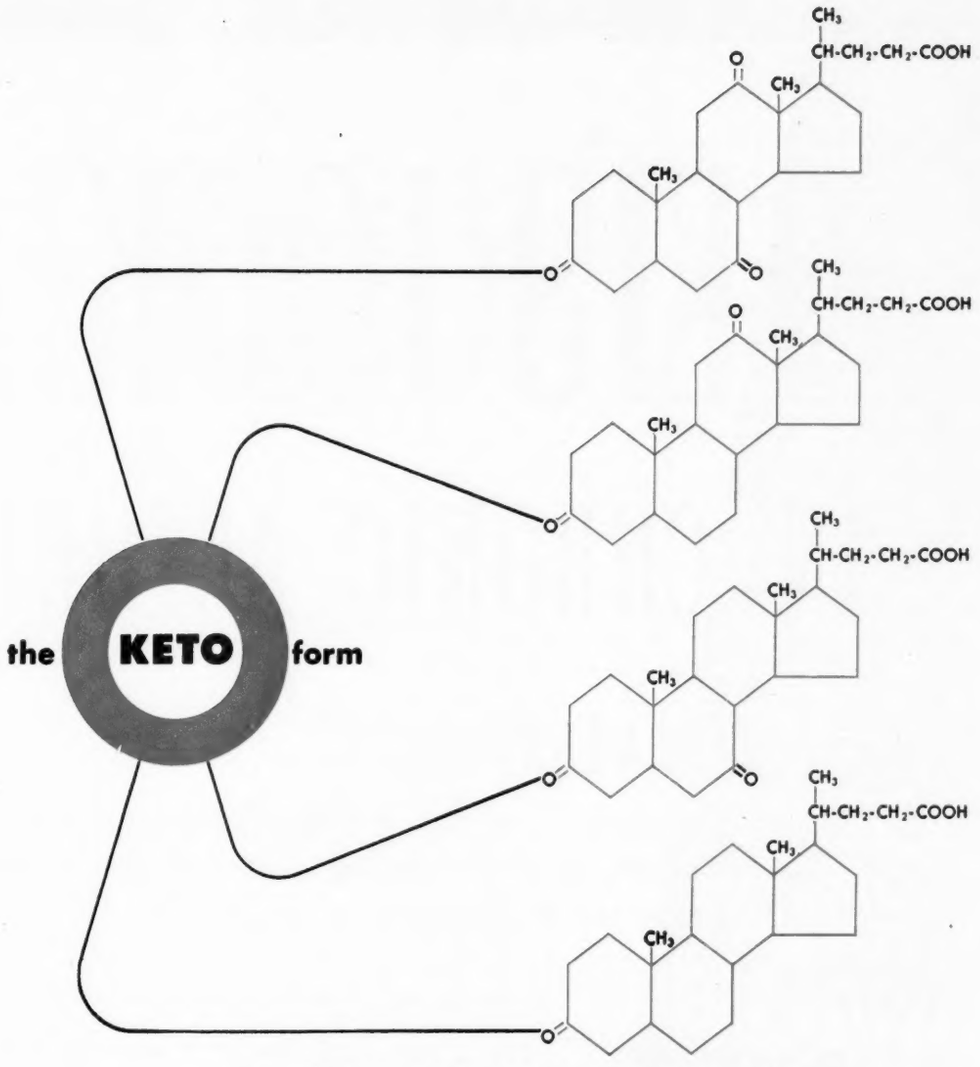
**Medicine in the Changing Order.** Report of the New York Academy of Medicine Committee on Medicine and The Changing Order. Pp. 232. New York, 1947. The Commonwealth Fund. *Price* $2.00.

"Medicine in the Changing Order" is a carefully prepared, comprehensive report of the results of a well planned study by a committee whose objective was "to be informed on the nature, quality and direction of the economic and social changes that are taking place now and that are clearly forecast for the immediate future; to define in particular how these changes are likely to affect medicine in its various aspects; to determine how the best elements in the science of medicine and in its services to the public may be preserved and embodied in whatever new social order may ultimately develop." The composition of the committee is of interest in that it is representative of various lay groups, such as insurance companies, social welfare, labor, industry, the ministry and law, physicians interested in medical education and public health and dentistry and nursing.

The report begins with a chapter briefly reviewing the history of American medicine. It passes on to medicine in the last decades and an estimate of the health of the nation at the present time, emphasizing wide regional differences. The succeeding chapters, covering medical care, preventive medicine, the hospital, nursing and medical insurance, contain calculated estimates of the faults and benefits of the existing institutions, or the lack of them, with specific suggestions in each instance as to how remedies and improvements may be effected. For ready reference there is a summary at the end of most chapters listing the proposed changes. The final chapter entitled "The Method and The Goal" is a summary of the ideals and conditions which are attendant upon good medical care.

The conclusions of the Committee are admirable. They are of particular interest in this time of increasing socialization. Socialized medicine is rejected in favor of voluntary pre-payment plans plus government aid. The importance of the cooperation of physicians is realized and the inefficiency of bureaucratic administration is deprecated. This critical study is, in the opinion of this reader, not only of general interest but should be required reading for politicians and members of the medical profession.

B. H.

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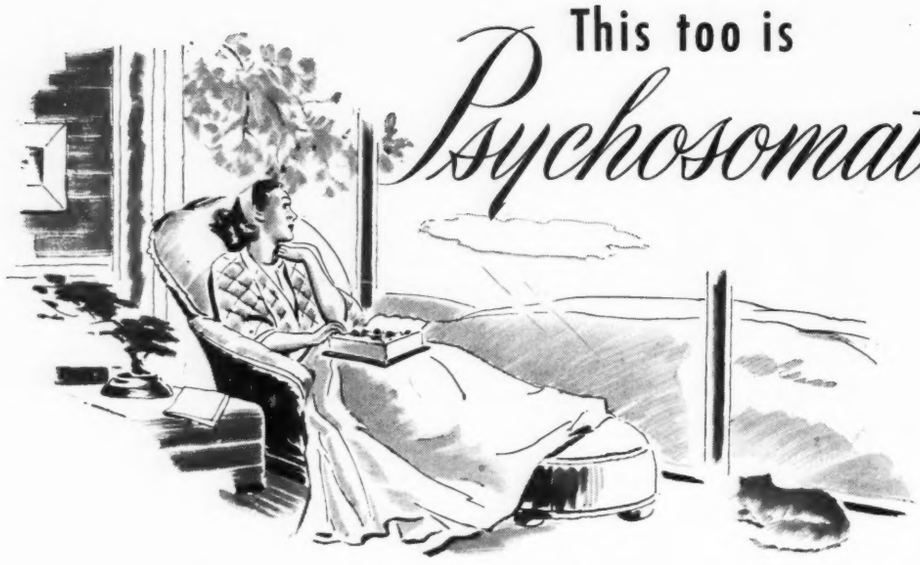

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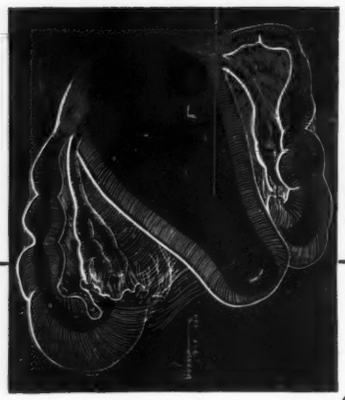
# Hope for  the "pelvic cripple"...

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> This baby was desperately sick when first seen—depleted from food loss and the exhaustion of violent coughing. She was put under oxygen, and although the case looked pretty hopeless, injections of Hypertussis were given—with remarkable results. The paroxysms decreased rapidly and the infant began to respond to general therapy.

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> At the AMA Section on Pediatrics, an outstanding paper on whooping cough serums concluded with this statement: "Our results suggest that human hyperimmune serum or globulin should be used in the treatment of all infants who are seriously ill with whooping cough." *1.*
>
> Another study on *the use of Hypertussis in 26 uncomplicated cases* reports: "Results of treatment were considered excellent in 14, good in 4, moderate in 4, and equivocal in 4. No patient became worse or died. Very striking was the fact that no patient in this group developed pneumonia or any other complication of pertussis . . ." *2.*

**If you'd like to read the complete articles, write for reprints.**

*Your C.D.M.*

(Cutter Detail Man)

*1. Kohn, Fischer, et al., Am. Jour. Dis. Child. Sept., 1947*

*2. Brainerd, Henry, Jour. Ped. Jan., 1948*

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# High Potency *plus* Stability

## Principal B Vitamins
## Stable Soluble Powder

The golden powder avidly accepts aqueous diluent, instantly forms full potency vitamin solution ready to inject in whatever dosage the physician's judgment demands.

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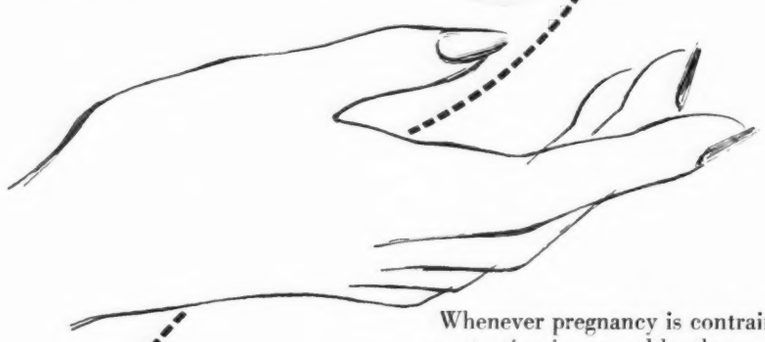

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Whenever pregnancy is contraindicated, maximal protection is assured by the new Lanteen technique. This NEW TECHNIQUE gives dual protection—the mechanical protection of the Lanteen Flat Spring Diaphragm plus the spermatocidal activity of Lanteen Jelly.

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Not only does Dexedrine produce striking improvement in mood and outlook—but, because of the unique "smoothness" of its action, it spares the patient the disturbing consciousness of "drug stimulation."
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**the central nervous stimulant of choice** (*dextro-amphetamine sulfate, S. K. F.*)

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**Custom-made clots are now available with Gelfoam.***

The old surgeon may have dreamed of the day when a ready-made clot would staunch oozing surfaces, capillary bleeding, trickling from small veins, hemorrhage from resected tissues.

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1. Gusberg, S. B., Am. J. Obst. & Gyn. 50:902, 1945.

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